10/463,173

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NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	JUL 12	BEILSTEIN enhanced with new display and select options, resulting in a closer connection to BABS
NEWS	4	AUG 02	IFIPAT/IFIUDB/IFICDB reloaded with new search and display fields
NEWS	5	AUG 02	CAplus and CA patent records enhanced with European and Japan Patent Office Classifications
NEWS	6	AUG 02	The Analysis Edition of STN Express with Discover! (Version 7.01 for Windows) now available
NEWS	7	AUG 27	BIOCOMMERCE: Changes and enhancements to content coverage
NEWS	8	AUG 27	BIOTECHABS/BIOTECHDS: Two new display fields added for legal status data from INPADOC
NEWS	9	SEP 01	INPADOC: New family current-awareness alert (SDI) available
NEWS	10	SEP 01	New pricing for the Save Answers for SciFinder Wizard within STN Express with Discover!
NEWS	11	SEP 01	New display format, HITSTR, available in WPIDS/WPINDEX/WPIX
NEWS	12	SEP 27	STANDARDS will no longer be available on STN
NEWS	13	SEP 27	SWETSCAN will no longer be available on STN
NEWS	14	OCT 28	KOREAPAT now available on STN

NEWS EXPRESS	OCTOBER 29 CURRENT WINDOWS VERSION IS V7.01A, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 11 AUGUST 2004
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
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NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

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=> fil reg
COST IN U.S. DOLLARS SINCE FILE ENTRY TOTAL SESSION

FULL ESTIMATED COST 0.21 0.21

FILE 'REGISTRY' ENTERED AT 21:44:32 ON 14 NOV 2004
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DICTIONARY FILE UPDATES: 12 NOV 2004 HIGHEST RN 780001-49-2

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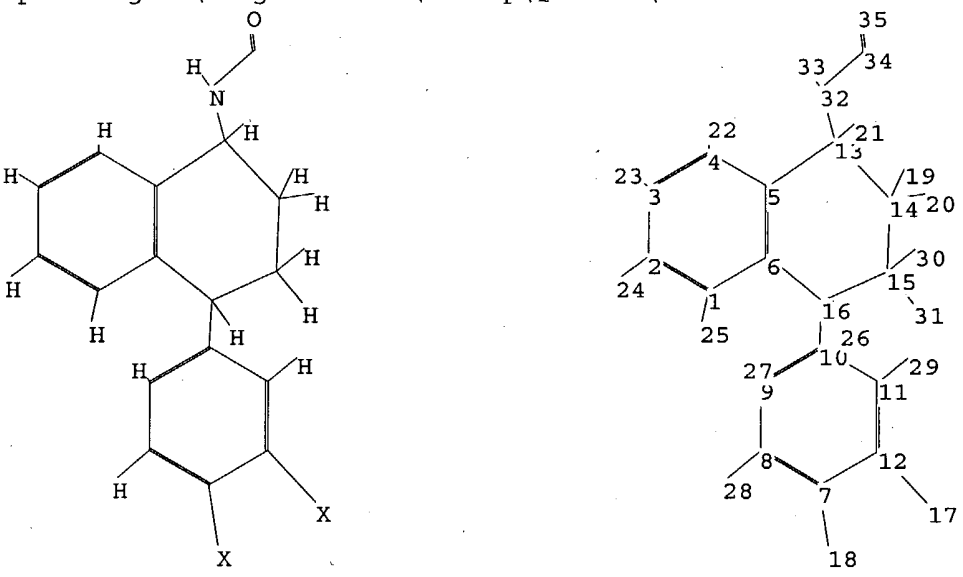
=>
Uploading C:\Program Files\Stnexp\Queries\10663173.str



chain nodes :
17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
chain bonds :
1-25 2-24 3-23 4-22 7-18 8-28 9-27 10-16 11-29 12-17 13-21 13-32 14-19
14-20 15-30 15-31 16-26 32-33 32-34 34-35
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-13 6-16 7-8 7-12 8-9 9-10 10-11 11-12 13-14
14-15 15-16
exact/norm bonds :
5-13 6-16 13-14 13-32 14-15 15-16 32-34 34-35
exact bonds :

1-25 2-24 3-23 4-22 7-18 8-28 9-27 10-16 11-29 12-17 13-21 14-19 14-20
15-30 15-31 16-26 32-33
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:CLASS 18:CLASS 19:CLASS
20:CLASS 21:CLASS 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS
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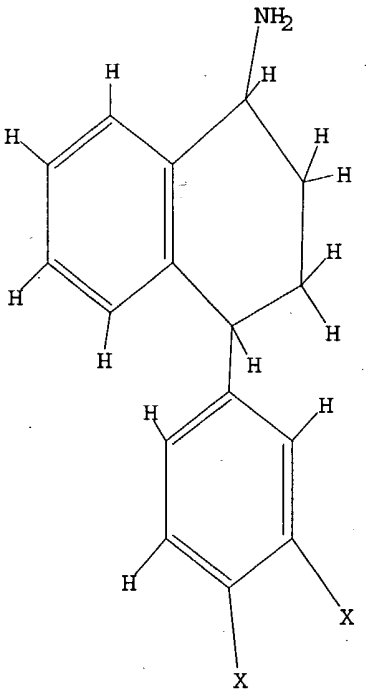
L1 STRUCTURE UPLOADED

=> d query
L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> s l1
SAMPLE SEARCH INITIATED 21:44:49 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 1918 TO ITERATE

52.1% PROCESSED 1000 ITERATIONS 0 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 35733 TO 40987
PROJECTED ANSWERS: 0 TO 0

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L2             0 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 21:44:52 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -  38243 TO ITERATE

100.0% PROCESSED   38243 ITERATIONS                              12 ANSWERS
SEARCH TIME: 00.00.01

L3            12 SEA SSS FUL L1

=> fil caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                   155.42     155.63

FILE 'CAPLUS' ENTERED AT 21:44:55 ON 14 NOV 2004
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FILE COVERS 1907 - 14 Nov 2004  VOL 141 ISS 21
FILE LAST UPDATED: 12 Nov 2004  (20041112/ED)

 This file contains CAS Registry Numbers for easy and accurate
  substance identification.


=> s l3
L4             79 L3

=> d l4 1-79 abs ibib hitstr
```

L4 ANSWER 1 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB The serotonin transporter (SERT) belongs to a family of sodium chloride-dependent transporters responsible for uptake of amino acids and biogenic amines from extracellular spaces. SERT represents the main pharmacol. target in the treatment of several clin. conditions, including depression and anxiety. Serotonin-selective reuptake inhibitors and tricyclic antidepressants are the most predominantly prescribed drugs in the treatment of depression. In addition to antidepressants also psychostimulants, like cocaine and amphetamines, are important SERT antagonists. In the present study, the authors report the cloning and characterization of chicken SERT. Although the uptake kinetic was very similar to human SERT, the pharmacol. profiles differed considerably for the two species. The authors find that chicken SERT is capable of discriminating between different serotonin-selective reuptake inhibitors; thus, the potency of S-citalopram and paroxetine is reduced more than 40-fold. A cross-species chimera strategy was undertaken and followed by species-scanning mutagenesis. Differences in pharmacol. profiles were tracked to amino acid residues 169, 172, and 586 in human SERT. Structure-activity studies on structurally related compds. indicated that species divergences in drug sensitivity between human and chicken SERT were arising from differences in coordination or recognition of an important aminomethyl pharmacophoric substructure, which is shared by all high affinity antidepressants. Consequently, the authors suggest that Ala169 and Ile172 of human SERT are important residues in sensing the N-methylation state of SERT antagonists.

ACCESSION NUMBER: 2004:791467 CAPLUS

TITLE: The Chicken Serotonin Transporter Discriminates between Serotonin-selective Reuptake Inhibitors: A Species-scanning mutagenesis study

AUTHOR(S): Larsen, Mads Breum; Elfving, Betina; Wiborg, Ove

CORPORATE SOURCE: Laboratory of Molecular Neurobiology, Department of Biological Psychiatry, Aarhus Psychiatric University Hospital, Risskov, 8240, Den.

SOURCE: Journal of Biological Chemistry (2004), 279(40), 42147-42156
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

IT INDEXING IN PROGRESS

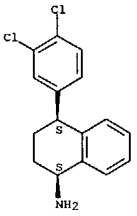
IT **87857-41-8**, Desmethylsertraline
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(chicken serotonin transporter discriminates between serotonin-selective reuptake inhibitors, a Species-scanning mutagenesis study)

RN 87857-41-8 CAPLUS

CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 1 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB Sertraline and paroxetine are frequently prescribed SSRIs for long-term treatment of major depression. Nevertheless, continuous follow-ups of drug concns. prevailing in patients during the whole treatment period are not available. Hence, in a large phase IV clin. trial, a total of 353 patients with major depression were enrolled for a 6-mo comparison of sertraline (50-150 mg daily) and paroxetine (20-60 mg daily). The present study reports the pharmacokinetic results of up to eight serum samples per patient. 1. A profound variability was found in the interindividual steady state and trough serum levels of sertraline, desmethylsertraline and paroxetine: the coefficient of variation (CV) was 59% for sertraline, 51% for desmethylsertraline, 27% for the ratio desmethylsertraline/sertraline (50 mg/day), and 71% for paroxetine (20 mg/day). The intraindividual CV for the ratio desmethylsertraline/sertraline was only 19%, indicating intraindividual metabolizing stability over time. Both sertraline and paroxetine displayed sex differences in the dose-concentration correlation. 2. It was possible to predict sertraline, but not paroxetine, steady state levels. 3. The terminal elimination t1/2 for both drugs after 6 mo of treatments was similar to data previously reported from short-term withdrawal studies. 4. No correlation between serum drug concns. and clin. effect was detected for either sertraline or paroxetine. For the future, continuous efforts are warranted to perform PK investigations in the natural clin. setting in which the drugs are usually prescribed.

ACCESSION NUMBER: 2004:682102 CAPLUS

DOCUMENT NUMBER: 141:342815

TITLE: Serum disposition of sertraline, N-desmethylsertraline and paroxetine: A pharmacokinetic evaluation of repeated drug concentration measurements during 6 months of treatment for major depression

AUTHOR(S): Reis, Margareta; Aberg-Wistedt, Anna; Agren, Hans; Hoeglund, Peter; Akerblad, Ann-Charlotte; Bengtsson, Finn

CORPORATE SOURCE: Department of Medicine and Care, Division of Clinical Pharmacology, Faculty of Health Sciences, Linkoeping University, Linkoeping, Swed.

SOURCE: Human Psychopharmacology (2004), 19(5), 283-291
CODEN: HUPSEC; ISSN: 0885-6222

PUBLISHER: John Wiley & Sons Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

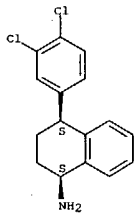
IT **87857-41-8**, N-Desmethylsertraline
RL: PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(serum disposition of sertraline, desmethylsertraline and paroxetine)

RN 87857-41-8 CAPLUS

CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 2 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

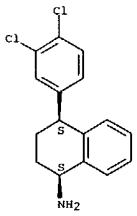
AB The 1st indication that select antidepressants and their metabolites accumulate in organisms residing in effluent-dominated streams was provided. Fluoxetine, norfluoxetine, sertraline, and desmethylsertraline were detected in brain, liver, and lateral muscle tissues of 3 fish populations, Lepomis macrochirus (bluegill), Ictalurus punctatus (channel catfish) and Pomoxis nigromaculatus (black crappie). The highest concns. of all compds. were observed in brain and liver; lowest concns. were detected in lateral muscle. Fish with larger body size such as I. punctatus and P. nigromaculatus generally accumulated higher amts. of all the compds. tested.

ACCESSION NUMBER: 2004:613535 CAPLUS
DOCUMENT NUMBER: 141:230101
TITLE: Determination of select antidepressants in organisms from a municipal effluent-dominated stream
AUTHOR(S): Brooks, Bryan W.; Chambliss, C. Kevin; Stanley, Jacob K.; Ramirez, Alejandro; Banks, Kenneth; Johnson, Robert D.; Lewis, Russell J.
CORPORATE SOURCE: Department of Environmental Studies, Center for Reservoir and Aquatic Systems Research, Baylor University, Waco, TX, 76798, USA
SOURCE: Preprints of Extended Abstracts presented at the ACS National Meeting, American Chemical Society, Division of Environmental Chemistry (2004), 44(2), 1351-1355
CODEN: PEACF2; ISSN: 1524-6434
PUBLISHER: American Chemical Society, Division of Environmental Chemistry
DOCUMENT TYPE: Journal; (computer optical disk)
LANGUAGE: English

IT **87857-41-8**, Desmethylsertraline
RL: POL (Pollutant); OCCU (Occurrence)
(antidepressants in fish from municipal effluent-dominated streams)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L4 ANSWER 3 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

L4 ANSWER 4 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB The invention provides compns. and methods for the treatment of a vaso-occlusive event. More particularly, the invention provides a combination therapy for the treatment of a vaso-occlusive event comprising the administration to a subject of a selective serotonin reuptake inhibitor in combination with a cyclooxygenase-2 selective inhibitor.

ACCESSION NUMBER: 2004:565129 CAPLUS
DOCUMENT NUMBER: 141:99705
TITLE: Methods and compositions using cyclooxygenase-2 selective inhibitors and selective serotonin reuptake inhibitors for the treatment or prevention of a vaso-occlusive event
INVENTOR(S): Stephenson, Diane T.; Taylor, Duncan P.
PATENT ASSIGNEE(S): Pharmacia Corporation, USA
SOURCE: PCT Int. Appl., 159 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004058354	A1	20040715	WO 2003-US40955	20031222
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004171664	A1	20040902	US 2003-743485	20031222
PRIORITY APPLN. INFO.:			US 2002-435078P P	20021220

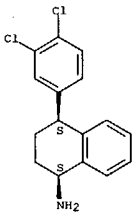
OTHER SOURCE(S): MARPAT 141:99705

IT **87857-41-8**, N-Demethylsertraline
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase 2 selective inhibitors and selective serotonin reuptake inhibitors for treatment or prevention of vaso-occlusive event)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 4 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L4 ANSWER 5 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB Background: Selective serotonin reuptake inhibitor antidepressants (SSRIs) and benzodiazepines are frequently used to treat maternal depression and anxiety disorders during pregnancy. Recent reports suggest that prenatal SSRI exposure is associated with a neonatal discontinuation syndrome. It remains unclear whether these symptoms are directly related to SSRI exposure alone or are due to concurrent pharmacol. factors. Also, this study explores relationships between neonatal outcomes and medication levels during pregnancy, at delivery, and in the newborn period. Method: This study sought to compare newborn behavior following second and third trimester exposure to either single-agent SSRIs (group 1) or SSRIs combined with clonazepam (group 2). A prospective cohort of mothers and their infants (N = 46) who had received SSRI medication alone or in combination with clonazepam were studied from June 1996 through June 2000 and compared with a non-exposed control group (N = 23). Infants were assessed in the newborn period for signs suggestive of a "discontinuation syndrome.". Maternal drug levels were measured during the pregnancy and at delivery. Infant drug levels from cord blood and at day 2 of life were also obtained. Results: Overall, 30% of the exposed infants (groups 1 and 2, N = 14) showed symptoms of transient poor neonatal adaptation compared with 9% (N = 2) of control infants. In group 1, 25% had symptoms (fluoxetine N = 3; paroxetine N = 3; sertraline N = 1) and in group 2, 39% of infants had symptoms (paroxetine with clonazepam, N = 7). Symptoms were typically mild respiratory distress and, less commonly, hypotonia. Symptoms were self limited and not associated with other neonatal conditions. When paroxetine was combined with clonazepam, infants with symptoms had significantly elevated paroxetine levels when compared with similarly exposed infants without symptoms ($p < .05$). Among single-agent paroxetine-exposed infants, drug levels did not differ significantly between those with and without symptoms. Maternal dose of clonazepam was significantly higher ($p < .05$) during pregnancy and at delivery among symptomatic infants compared with non-symptomatic infants. Developmental outcomes at 2 and 8 mo of age did not differ between symptomatic and non-symptomatic infants. Conclusion: While transient neonatal symptoms were found in infants after single-agent prenatal exposure to SSRIs and when paroxetine was combined with clonazepam, the addition of clonazepam appeared to alter paroxetine metabolism, leading to increased drug levels and risk for transient neonatal symptoms. These data highlight the importance of accounting for a variety of pharmacol. factors beyond single-agent SSRI exposure that may lead to poor neonatal adaptation. Further studies are needed with a larger sample of infants to determine the role of clonazepam and whether similar outcomes occur when exposure includes other SSRIs in combination with clonazepam.

ACCESSION NUMBER: 2004:281036 CAPLUS
DOCUMENT NUMBER: 140:314965
TITLE: Pharmacologic factors associated with transient neonatal symptoms following prenatal psychotropic medication exposure
AUTHOR(S): Oberlander, Tim F.; Misri, Shaila; Fitzgerald, Colleen E.; Kostaras, Xanthoula; Rurak, Dan; Riggs, Wayne

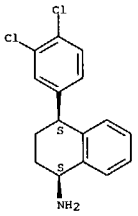
L4 ANSWER 5 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

CORPORATE SOURCE: Department of Pediatrics, University of British Columbia, Vancouver, BC, Can.
SOURCE: Journal of Clinical Psychiatry (2004), 65(2), 230-237
CODEN: JCLPDE; ISSN: 0160-6689
PUBLISHER: Physicians Postgraduate Press, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, Desmethylsertraline
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. factors associated with transient neonatal symptoms following prenatal psychotropic medication exposure)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB Trans-, (1R,4S)-, and (1S,4R)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamines are claimed. In functional monoamine uptake inhibition assays for serotonin, norepinephrine, and dopamine, the (1R,4S)- isomer showed IC50 = 0.0077, 0.0096, and 0.0064 μM, resp.

ACCESSION NUMBER: 2004:252469 CAPLUS
DOCUMENT NUMBER: 140:287185
TITLE: Preparation of trans-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine for treatment of CNS disorders.
INVENTOR(S): Jerussi, Thomas P.; Fang, Qun Kevin; Currie, Mark
PATENT ASSIGNEE(S): Sepracor, Inc., USA
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004024669	A1	20040325	WO 2003-US29110		20030916
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2004092605	A1	20040513	US 2003-663173		20030916
PRIORITY APPLN. INFO.:			US 2002-411304P	P	20020916
			US 2002-411305P	P	20020916

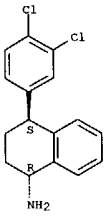
OTHER SOURCE(S): CASREACT 140:287185

IT **675126-04-2P**, trans-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine **675126-05-3P**, (1R,4S)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine **675126-06-4P**, (1S,4R)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine **675126-07-5P**, (1S,4R)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride **675126-08-6P**, (1R,4S)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride **675126-09-7P**, (1R,4R)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride **675126-10-0P**, (1S,4S)-4-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine hydrochloride
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of dichlorophenyltetrahydronaphthalenamines for treatment of CNS disorders)

RN 675126-04-2 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1R,4S)-rel- (9CI) (CA INDEX NAME)

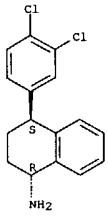
L4 ANSWER 6 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

Relative stereochemistry.



RN 675126-05-3 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1R,4S)-(9CI) (CA INDEX NAME)

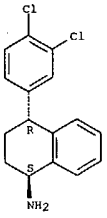
Absolute stereochemistry.



RN 675126-06-4 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4R)-(9CI) (CA INDEX NAME)

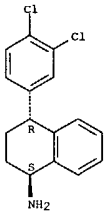
Absolute stereochemistry.

L4 ANSWER 6 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RN 675126-07-5 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, hydrochloride, (1S,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

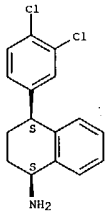


● HCl

RN 675126-08-6 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, hydrochloride, (1R,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 6 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

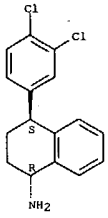


● HCl

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

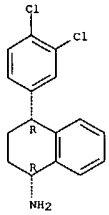
L4 ANSWER 6 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



● HCl

RN 675126-09-7 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, hydrochloride, (1R,4R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● HCl

RN 675126-10-0 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, hydrochloride, (1S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 7 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB Methods and compns. for reducing or controlling appetite using cyclooxygenase-2 inhibitors are disclosed.

ACCESSION NUMBER: 2004:100963 CAPLUS
DOCUMENT NUMBER: 140:139550
TITLE: Cyclooxygenase-2 inhibitors for appetite suppression
INVENTOR(S): Schwartz, Yael
PATENT ASSIGNEE(S): Sepracor Inc., USA
SOURCE: PCT Int. Appl., 10 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004010955	A2	20040205	WO 2003-US23922	20030731
WO 2004010955	A3	20040805		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU

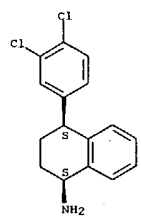
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-399976P P 20020731

IT **87857-41-8**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclooxygenase-2 inhibitors for appetite suppression, and use with other agents)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

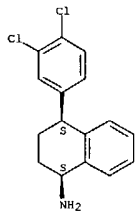


L4 ANSWER 7 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

L4 ANSWER 8 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB The high incidence of psychiatric illness in the postpartum period and the increasing percentage of women who breastfeed has focused attention on the treatment of breastfeeding women with psychotropic medications and, addnl., the exposure of nursing infants to these medications. Consequently, there has been an increased effort to develop standardized methods for quantifying psychotropic medications in breast milk. This paper details a novel method for quantifying the concns. of multiple selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) in breast milk. The method consists of a common liquid/liquid and solid-phase extraction followed by HPLC separation on a common column and UV detection. Assay system 1 measures fluoxetine, norfluoxetine, fluvoxamine, and paroxetine; assay 2 measures sertraline and desmethylsertraline; and assay 3 measures the TCAs including doxepin, nordoxepin, desipramine, imipramine, nortriptyline, and amitriptyline. The method is shown to be a highly accurate and precise technique for measuring 12 different antidepressants in human breast milk and to be free of the matrix effects often encountered in breast milk drug analyses.
ACCESSION NUMBER: 2004:42859 CAPLUS
DOCUMENT NUMBER: 141:167098
TITLE: A Novel System for the Determination of Antidepressant Concentrations in Human Breast Milk
AUTHOR(S): Hostetter, Amy L.; Stowe, Zachary N.; Cox, Mary; Ritchie, James C.
CORPORATE SOURCE: Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, 30322, USA
SOURCE: Therapeutic Drug Monitoring (2004), 26(1), 47-52
CODEN: TDMODV; ISSN: 0163-4356
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: ANT (Analyte); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(assay system II of novel technique consisiting liquid/liquid and solid-phase extraction followed by HPLC separation and UV detection accurately and precisely determined concentration of desmethylsertraline in human breast milk)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 8 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

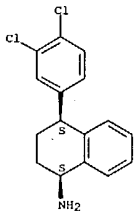


REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Introduction: Selective serotonin reuptake inhibitors (SSRIs) are popularly prescribed for treating depression. With a few exceptions, these psychotropic medications are not approved by aeromedical regulatory authorities for use by aviators. Since SSRIs have the potential for impairing performance and causing drug-drug interactions, the prevalence of SSRIs in pilot fatalities of civil aviation accidents was evaluated. Methods: Postmortem samples from pilots involved in fatal civil aircraft accidents are submitted to the Civil Aerospace Medical Institute (CAMI) for toxicol. evaluation. Findings from such evaluations are maintained in the CAMI Toxicol. Database. This database was examined for the presence of SSRIs in pilot fatalities of the accidents that occurred during 1990-2001.
Results: Out of 4,184 fatal civil aviation accidents from which CAMI received samples, there were 61 accidents in which pilot fatalities had SSRIs. Of these accidents, 56 were of the general aviation category, 2 were of the air taxi and commuter category, 2 were of the agricultural category, and 1 was of the ultralight category. Blood concns. of SSRIs in the fatalities were 11-1121 ng · ml-1 for fluoxetine; 47-13102 ng · ml-1 for sertraline; 68-1441 ng · ml-1 for paroxetine; and 314-462 ng · ml-1 for citalopram. In 39 of the 61 pilots, other drugs-for example, analgesics, anti histaminics, benzodiazepines, narcotic analgesics, and/or sympathomimetics-and/or ethanol were also present. As determined by the National Transportation Safety Board, the use of an SSRI [with or without other drugs) and/or ethanol] has been a contributory factor in at least 9 of the 61 accidents. Conclusions: Nos. of SSRI-involved accidents were low, and blood SSRI concns. in the associated pilot fatalities ranged from subtherapeutic to toxic levels. However, the interactive effects of other drug(s), ethanol, and/or even altitude hypoxia in producing adverse effects in the pilots cannot be ruled out. Findings from this study should be useful in investigating SSRI and other substance-involved accidents and in making decisions concerning the use of SSRIs in aviation.
ACCESSION NUMBER: 2003:988335 CAPLUS
DOCUMENT NUMBER: 141:2479
TITLE: Selective serotonin reuptake inhibitors in pilot fatalities of civil aviation accidents, 1990-2001
AUTHOR(S): Akin, Ahmet; Chaturvedi, Arvind K.
CORPORATE SOURCE: Bioaeronautical Sciences Research Laboratory, Aerospace Medical Research Division, Civil Aerospace Medical Institute, U.S. Department of Transportation, Federal Aviation Administration, Oklahoma City, USA
SOURCE: Aviation, Space and Environmental Medicine (2003), 74(11), 1169-1176
CODEN: ASEMCG; ISSN: 0095-6562
PUBLISHER: Aerospace Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: ADV (Adverse effect, including toxicity); ANT (Analyte); ANST (Analytical study); BIOL (Biological study)
(serotonin reuptake inhibitors in pilot fatalities of civil aviation

L4 ANSWER 9 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
accidents, 1990-2001)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 10 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB The invention discloses pharmacol. methods for the prevention of amelioration of sleep-related breathing disorders via administration of agents or combinations of agents that possess serotonin-related pharmacol.
activity. Agents of the invention include e.g. ondansetron.
ACCESSION NUMBER: 2003:532342 CAPLUS
DOCUMENT NUMBER: 139:95476
TITLE: Agents having serotonin-related pharmacol. activity for the pharmacological treatment of sleep apnea and other sleep-related breathing disorders
INVENTOR(S): Radulovacki, Miodrag; Carley, David W.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 20 pp., Cont.-in-part of U.S. Ser. No. 16,901.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003130266	A1	20030710	US 2002-285277	20021031
US 2002086870	A1	20020704	US 2001-16901	20011214
US 6727242	B2	20040427		
WO 2004041272	A2	20040521	WO 2003-US34592	20031029
WO 2004041272	A3	20040916		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

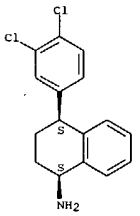
PRIORITY APPLN. INFO.:

US 2001-16901	A2	20011214
US 1998-76216P	P	19980227
WO 1999-US4347	W	19990226
US 2000-622823	A1	20000823
US 2002-285277	A	20021031

IT **87857-41-8**, Demethylsertraline
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(agents with serotonin-related pharmacol. activity for treatment of sleep apnea and other sleep-related breathing disorders)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

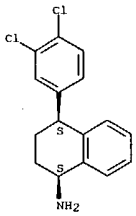
L4 ANSWER 10 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L4 ANSWER 11 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Pharmacokinetic drug-drug interactions often occur at the level of P-glycoprotein (Pgp). To study possible interactions caused by the newer antidepressants we investigated citalopram, fluoxetine, fluvoxamine, paroxetine, reboxetine, sertraline, and venlafaxine and their major metabolites desmethylcitalopram, norfluoxetine, paroxetine-metabolite (paroxetine-M), desmethylsertraline, N-desmethylvenlafaxine, and O-desmethylvenlafaxine for their ability to inhibit Pgp. Pgp inhibition was studied by a fluorometric assay using calcein-acetoxymethylester as Pgp substrate and two different cell systems: L-MDR1 cells (model for human Pgp) and primary porcine brain capillary endothelial cells (pBCECs, model for the blood-brain barrier). Both cell systems proved to be suitable for the evaluation of Pgp inhibitory potency of drugs. All antidepressants tested except O-desmethylvenlafaxine showed Pgp inhibitory
activity with sertraline, desmethylsertraline, and paroxetine being the most potent, comparable with the well known Pgp inhibitor quinidine. In L-MDR1 cells fluoxetine, norfluoxetine, fluvoxamine, reboxetine, and paroxetine-M revealed intermediate Pgp inhibition and citalopram, desmethylcitalopram, venlafaxine, and N-desmethylvenlafaxine were only weak inhibitors. The ranking order was similar in pBCECs. The fact that some of the compds. tested exert Pgp inhibitor effects at similar concns. as quinidine suggests that pharmacokinetic drug-drug interactions between the newer antidepressants and Pgp substrates should now be thoroughly studied in vivo.
ACCESSION NUMBER: 2003:262485 CAPLUS
DOCUMENT NUMBER: 139:207091
TITLE: Inhibition of P-glycoprotein by newer antidepressants
AUTHOR(S): Weiss, Johanna; Dormann, Sven-Maria Gregor; Martin-Facklam, Meret; Kerpen, Christian Johannes; Ketabi-Kiyanvash, Nahal; Haefeli, Walter Emil
CORPORATE SOURCE: Department of Internal Medicine VI, Clinical Pharmacology, and Pharmacoepidemiology, University of Heidelberg, Heidelberg, Germany
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2003), 305(1), 197-204
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antidepressant inhibition of P-glycoprotein in relation to pharmacokinetic drug interactions)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

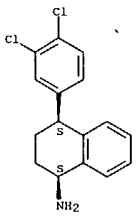
L4 ANSWER 11 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 12 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
IT **87857-41-8**, Desmethylsertraline
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(pharmacokinetics of sertraline excretion into human breast milk as predictors of infant serum concns.)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



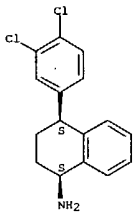
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 12 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Background: The purpose of this study was to attain a new landmark in the area of selective serotonin reuptake inhibitor therapy during lactation by establishing a basis for interpreting infant serum concns. and for minimizing infant exposure in the absence of treatment-emergent side effects. Method: Breast milk and paired maternal and infant sera were collected following maternal treatment with sertraline monotherapy (25-200 mg/day) administered once daily. Sertraline and its major metabolite were measured in breast milk and serum samples using high-performance liquid chromatog. with UV detection (limit of detection = 2 ng/mL). Results: Twenty-six nursing women with DSM-IV major depressive disorder participated in the study; the mean (SD) daily sertraline dose was 123.9 (62.8) mg/day. Fifteen women submitted 182 breast milk samples for anal. of gradient (foremilk to hindmilk) and time course of medication excretion. The milk/plasma ratio was highly variable (range, 0.42–4.81). A significant gradient and time course of excretion for both sertraline (p < .001 for both) and desmethylsertraline (p < .001 for gradient and p < .046 for time course) were observed, with the highest concns. observed in the hindmilk 8 to 9 h after maternal ingestion. Math. modeling of sertraline and desmethylsertraline excretion revealed that discarding breast milk 9 h after maternal dose decreased the infant daily dose of sertraline by a mean of 17.1% (1.8%). Twenty-two mother/infant sera pairs were obtained. Sertraline was detectable in 4 infants (18% of sample), and desmethylsertraline was found in 11 infants (50% of sample). The mean (SD) maximum calculated nursing infant dose of sertraline, 0.67 (0.61) mg/day, and desmethylsertraline, 1.44 (1.36) mg/day, represented 0.54% (0.49%) of the maternal daily dose. The maximum infant dose of desmethylsertraline (p < .002) significantly correlated with infant serum desmethylsertraline concns. (ng/mL). In contrast, maternal daily dose, duration of medication exposure, and infant age and weight at sampling did not correlate with either detectability (< 2 ng/mL vs. ≥ 2 ng/mL) or absolute concns. (ng/mL) in infant serum. No adverse events were reported or documented in any infant. Conclusion: These results extend previous studies by demonstrating the utility of breast milk anal. in interpreting infant serum concns. and minimizing infant exposure.
ACCESSION NUMBER: 2003:161587 CAPLUS
DOCUMENT NUMBER: 138:297064
TITLE: The pharmacokinetics of sertraline excretion into human breast milk: determinants of infant serum concentrations
AUTHOR(S): Stowe, Zachary N.; Hostetter, Amy L.; Owens, Michael J.; Ritchie, James C.; Sternberg, Kevan; Cohen, Lee S.; Nemeroff, Charles B.
CORPORATE SOURCE: Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA
SOURCE: Journal of Clinical Psychiatry (2003), 64(1), 73-80
CODEN: JCLPDE; ISSN: 0160-6689
PUBLISHER: Physicians Postgraduate Press, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

L4 ANSWER 13 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB The main purpose of this study was the investigation of quant. structure-activity relationships of serotonin transporter ligands with regard to the future development of potential new and selective PET radiotracers for the serotonin transporter. A heterogeneous data set of 19 selective and non-selective serotonin reuptake inhibitors was used. Affinity data for both the serotonin transporter and the norepinephrine transporter was available. As a necessary prerequisite for our 3D QSAR studies a reasonable alignment of the compds. was developed using GASP. It was based on an existing pharmacophore model. In addition to the widely used CoMFA method, the somewhat newer CoMSIA method was applied. Statistically reliable CoMFA models for both the serotonin transporter (q2=0.538) and the norepinephrine transporter (q2=0.445) were developed, further improving the internal predictability by applying region focusing for the serotonin transporter (q2=0.674). These models were compared with the CoMSIA models for the serotonin and the norepinephrine transporter that yielded comparable cross-validated correlation coeffs. (q2=0.531 and q2=0.502, resp.). Certain structural features that are distinctive of each transporter and important for high binding affinity were identified. Highly comparable results were obtained for CoMFA and CoMSIA. Both methods were applied to elucidate structural requirements for serotonin transporter selectivity. The resulting CoMSIA map provides important information for lead optimization with respect to selectivity enhancement.
ACCESSION NUMBER: 2003:109510 CAPLUS
DOCUMENT NUMBER: 139:159428
TITLE: 3D QSAR of serotonin transporter ligands: CoMFA and CoMSIA studies
AUTHOR(S): Wellsow, Julia; Machulla, Hans-Juergen; Kovar, Karl-Artur
CORPORATE SOURCE: Pharmaceutical Institute, University of Tubingen, Tubingen, 72076, Germany
SOURCE: Quantitative Structure-Activity Relationships (2002), 21(6), 577-589
CODEN: QSARDI; ISSN: 0931-8771
PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: PAC (Pharmacological activity); BIOL (Biological study)
(QSAR of serotonin transporter ligands)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 13 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

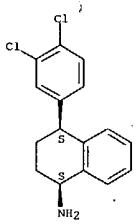


REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 14 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Separating drugs which are both polar and basic has long been difficult because
of the limited operating pH range of conventional HPLC columns. This paper describes a liquid chromatog. method capable of being used with either
diode-array or mass spectrometric detection for the identification and quantitation of 10 antidepressant and 2 antipsychotic drugs, all of which have serotonergic activity. In developing the method, the effects of varying buffers and mobile phase pH and of adding modifying agents on resolution and capacity factors were investigated. The organic buffers ammonia,
glycine, and triethylamine were each used in a mobile phase made up of 32.5% buffer/67.5% methanol (volume/volume) at a pH of 10.0. Addnl., 4 different concns. each of THF and acetonitrile were added to investigate the effect of a modifying agent on resolution and retention. In general, decreasing mobile phase pH reduced retention times and decreased resolution
Adding THF in place of the same amount of methanol tended to decrease retention times, and adding acetonitrile tended to slightly increase retention times. However, addition of both marginally improved resolution This
method was used to satisfactorily analyze brain, blood, liver, urine, vitreous fluid, and stomach contents in subjects known to have used these drugs. (c) 2003 Preston Publications.
ACCESSION NUMBER: 2003:70640 CAPLUS
DOCUMENT NUMBER: 138:315995
TITLE: LC-MS analysis of serotonergic drugs
AUTHOR(S): Goeringer, Kabrena E.; McIntyre, Iain M.; Drummer, Olaf H.
CORPORATE SOURCE: Victorian Institute of Forensic Medicine and Department of Forensic Medicine, Monash University, Southbank, 3006, Australia
SOURCE: Journal of Analytical Toxicology (2003), 27(1), 30-35
CODEN: JATOD3; ISSN: 0146-4760
PUBLISHER: Preston Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: ANT (Analyte); ANST (Analytical study)
(LC-MS anal. of serotonergic drugs)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 14 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

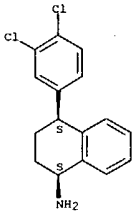


REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 15 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Bile is, in certain cases, collected together with blood from different sites (heart, brain, femoral), urine and other organs or matrixes. This study reports comparative results obtained from the anal. of blood and bile for different drugs found: acetaminophen, amphetamine and related compds., several antidepressants, several benzodiazepines, cocaine and its
metabolites, dextropropoxyphene and its metabolite, hydroxyzine, methadone
and metabolite, morphine and codeine, levomepromazine, thioridazine, propranolol, tramadol and its metabolite. Several findings are presented:
There were no significant differences in the levels of the compds. among the samples of blood obtained from different sites. Levels in bile are generally several fold higher than those in blood. The mean bile to blood
ratios vary from about 1 (for acetaminophen, amphetamine) to about 2000 (for desmethylclobazam). In certain cases (16 over 44), although the drug
or its metabolite was not detected in blood from different sites, it was detected in bile. As other authors had advocated, it is very useful to ask the pathologist to take the gall bladder with its contents together with the other samples, in order that the sample of bile can be used in the comprehensive toxicol. anal. and therefore be complementary to the other fluids or matrixes. An addnl. advantage for using bile is that the concns. of drugs or their metabolites are generally several fold higher than their blood concns.
ACCESSION NUMBER: 2002:669216 CAPLUS
DOCUMENT NUMBER: 138:164923
TITLE: Bile analysis of drugs in postmortem cases
AUTHOR(S): Vanbinst, R.; Koenig, J.; Di Fazio, V.; Hassoun, A.
CORPORATE SOURCE: St-Luc Hospital, Laboratory of Toxicology, Universite Catholique de Louvain, Brussels, 1200, Belg.
SOURCE: Forensic Science International (2002), 128(1-2), 35-40
CODEN: FSINDR; ISSN: 0379-0738
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(drug screening in bile compared with blood, urine, and gastric content
in forensic postmortem cases)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 15 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 16 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB Most drugs are excreted into breast milk to some extent and are bioavailable to the infant. The ability to predict the approx. amount of drug that might be present in milk from the drug structure would be very useful in the clin. setting. The aim of this research was to simplify and upgrade the previously developed model for prediction of the milk to plasma (M/P) concentration ratio, given only the mol. structure of the drug. The set of 123 drug compds., with exptl. derived M/P values taken from the literature, was used to develop, test and validate a predictive model. Each compound was encoded with 71 calculated mol. structure descriptors, including constitutional descriptors, topol. descriptors, mol. connectivity, geometrical descriptors, quantum chemical descriptors, physicochem. descriptors and liquid properties. Genetic algorithm was used to select a subset of the descriptors that best describe the drug transfer into breast milk and artificial neural network (ANN) to correlate selected descriptors with the M/P ratio and develop a QSAR. The averaged literature M/P values were used as the ANN's output and calculated mol. descriptors as the inputs. A nine-descriptor nonlinear computational neural network model has been developed for the estimation of M/P ratio values for a data set of 123 drugs. The model included the percent of oxygen, parachor, d., HOMO energy (HOMO), topol. indexes (χV2, χ2 and χ1) and shape indexes (κ3, κ2), as the inputs had four hidden neurons and one output neuron. The QSPR that was developed indicates that mol. size (parachor, d.) shape (topol. shape indexes, mol. connectivity indexes) and electronic properties (HOMO) are the most important for drug transfer into breast milk. Unlike previously reported models, the QSPR model described here does not require exptl. derived parameters and could potentially provide a useful prediction of M/P ratio of new drugs only from a sketch of their structure and this approach might also be useful for drug information service. Regardless of the model or method used to estimate drug transfer into breast milk, these predictions should only be used to assist in the evaluation of risk, in conjunction with assessment of the infant's response.

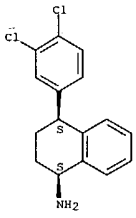
ACCESSION NUMBER: 2002:438488 CAPLUS
DOCUMENT NUMBER: 138:32765
TITLE: Molecular descriptors that influence the amount of drugs transfer into human breast milk
AUTHOR(S): Agatonovic-Kustrin, S.; Ling, L. H.; Tham, S. Y.; Alany, R. G.
CORPORATE SOURCE: School of Pharmaceutical, Molecular and Biomedical Science, University of South Australia, Adelaide, 5000, Australia
SOURCE: Journal of Pharmaceutical and Biomedical Analysis (2002), 29(1-2), 103-119
CODEN: JPBADA; ISSN: 0731-7085
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**
RL: PKT (Pharmacokinetics); PRP (Properties); BIOL (Biological study) (mol. descriptors that influence the amount of drugs transfer into human breast milk in relation to their bioavailability to the newborn)

L4 ANSWER 16 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 163 THERE ARE 163 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 17 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

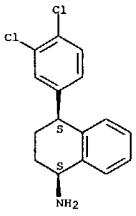
AB LC/MS/MS provides superior sensitivity and selectivity, rapid anal., maximized development efficiencies, and improved turnaround times. The challenges of large-scale LC/MS/MS anal. may be overcome with careful planning and the suggested troubleshooting techniques.

ACCESSION NUMBER: 2002:284366 CAPLUS
DOCUMENT NUMBER: 137:121824
TITLE: Systematic troubleshooting for LC/MS/MS
AUTHOR(S): Naidong, Weng; Halls, Timothy D. J.
CORPORATE SOURCE: Covance Laboratories Inc., Madison, WI, 53704, USA
SOURCE: Pharmaceutical Technology North America (2002), 26(3), 102,104,106,108,110,112,114,116,118,120
CODEN: PTNABQ; ISSN: 1534-2131
PUBLISHER: Advanstar Communications, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, Desmethyl-sertraline
RL: ANT (Analyte); ANST (Analytical study) (anal. of drugs in blood and urine by LC/MS/MS and troubleshooting techniques)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

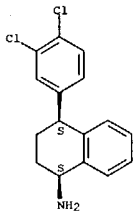


REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 18 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB LC/MS/MS provides superior sensitivity and selectivity, rapid anal., maximized development efficiencies, and improved turnaround times. The challenges of large-scale LC/MS/MS anal. may be overcome with careful planning and the suggested troubleshooting techniques. Part 1 presents troubleshooting techniques related to sample preparation and chromatog.

ACCESSION NUMBER: 2001:921013 CAPLUS
DOCUMENT NUMBER: 136:345886
TITLE: Systematic troubleshooting for LC/MS/MS Part 1: Sample preparation and chromatography
AUTHOR(S): Naidong, Weng; Halls, Timothy D. J.
CORPORATE SOURCE: Covance Laboratories Inc., Madison, WI, 53704, USA
SOURCE: BioPharm (Duluth, MN, United States) (2001), 14(11), 28,30,32,34,36,38
CODEN: BPRME5; ISSN: 1040-8304
PUBLISHER: Advanstar Communications, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: ANT (Analyte); ANST (Analytical study)
(sample preparation and anal. of drugs in human blood by LC/MS)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Screening methods which enable the selection of selective serotonin reuptake inhibitor compds. which do not possess significant inhibitory potency towards cytochrome P 450 enzymes, in particular, CYP2D6, are disclosed. The invention comprises a method of generating a pharmacophore model of selective serotonin reuptake inhibitor compds. which do not possess significant inhibitory potency towards CYP2D6. Methods for the discovery of selective serotonin reuptake inhibitor compds. which do not possess significant inhibitory potency towards the CYP2D6 enzyme are also disclosed. Pharmaceutical compns. comprising a selective serotonin reuptake inhibitor compound that does not possess significant inhibitory potency towards CYP2D6 as identified by methods of the invention are disclosed. The invention allow the uses of a selective serotonin reuptake inhibitor compound identified by the methods of the invention for the manufacture of medicaments and for the treatment of a condition, a disorder or a disease in a mammal for which such a selective serotonin reuptake inhibitor compound is therapeutically useful.

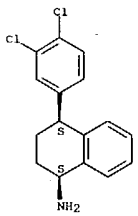
ACCESSION NUMBER: 2001:691818 CAPLUS
DOCUMENT NUMBER: 135:236399
TITLE: Pharmacophore models for the identification of the CYP2D6 inhibitory potency of selective serotonin reuptake inhibitors
INVENTOR(S): Ekins, Sean
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: Eur. Pat. Appl., 23 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1134290	A2	20010919	EP 2001-302116	20010308
EP 1134290	A3	20040102		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2002013372	A1	20020131	US 2001-804176	20010312
JP 2001324496	A2	20011122	JP 2001-72613	20010314
PRIORITY APPLN. INFO.:			US 2000-189099P P	20000314

IT **87857-41-8**, Desmethylsertraline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacophore models for identification of the CYP2D6 inhibitory potency of selective serotonin reuptake inhibitors)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 19 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L4 ANSWER 20 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB A method of treating asthma that includes the step of controlling the asthma by ingesting a composition which includes a selective serotonin reuptake inhibitor that is sertraline hydrochloride. Chronic administration of the sertraline thereof downregulates brain norepinephrine receptors. The increased output of the brain norepinephrine receptors increases the dilation of the bronchi. Sertraline has no significant affinity for adrenergic (alpha1, alpha2, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic (5HT1A, 5HT1B, 5HT2), or benzodiazepine receptors. Antagonism of such receptors has been hypothesized to be associated with various adverse anticholinergic, sedative, and cardiovascular effects.

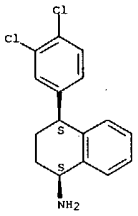
ACCESSION NUMBER: 2001:630896 CAPLUS
DOCUMENT NUMBER: 135:175371
TITLE: Composition for treating asthma with a serotonin reuptake inhibitor
INVENTOR(S): Ahmed, Magda Abdel Fattah
PATENT ASSIGNEE(S): USA
SOURCE: U.S., 6 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6281248	B1	20010828	US 2000-505747	20000216
PRIORITY APPLN. INFO.:			US 2000-505747	20000216

IT **87857-41-8**, N-Demethylsertraline
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(tablets containing sertraline for treating asthma)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

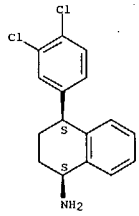
L4 ANSWER 20 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L4 ANSWER 21 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L4 ANSWER 21 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB Objective: The objective was to evaluate the relationship between the disposition of Sertraline and the presence of the CYP2C19 gene and to define the contribution of cytochrome P 450 2C19 (CYP2C19) to Sertraline N-demethylation. Methods: A single oral 100-mg dose of Sertraline was administered to 6 subjects who were extensive metabolizers and 6 subjects who were poor metabolizers recruited from 77 healthy Chinese volunteers whose genotypes were predetd. by polymerase chain reaction-based amplification, followed by restriction fragment length polymorphism anal. Phenotypes were determined by use of the omeprazole metabolic rate. The plasma concns. of Sertraline and desmethylsertraline were determined by gas chromatog. with electron-capture detection. Results: Six poor metabolizers with ml mutation had area under the plasma concentration vs. time curve (AUC0-∞) values (983.6 ± 199.3 μg • h/L vs. 697.6 ± 133.0 μg • h/L; P < 0.05) and terminal elimination half-life values of Sertraline (35.5 ± 5.6 h vs. 23.5 ± 4.4 h; P < 0.01) that were significantly higher than the values in 6 extensive metabolizers who were either homozygous or heterozygous for CYP2C19*1. The oral clearance of Sertraline in poor metabolizers (105.3 ± 19.4 L/h) was significantly lower than that of extensive metabolizers (148.4 ± 28.6 L/h). The area under the concentration-time curve from 0 to 144 h and the maximum plasma concentration of desmethylsertraline in poor metabolizers were significantly lower than the values of extensive metabolizers (627.6 ± 203.8 μg • h/L vs. 972.1 ± 270.3 μg • h/L; P < 0.05; and 23.6 ± 6.5 nmol/L vs. 32.4 ± 8.2 nmol/L; P < 0.01; resp.). Conclusions: The polymorphic CYP2C19 appears to be a major enzyme involved in the N-demethylation of Sertraline, and both extensive and poor metabolizers had marked differences in the disposition of Sertraline.

ACCESSION NUMBER: 2001:596898 CAPLUS
DOCUMENT NUMBER: 136:303912
TITLE: Pharmacokinetics of Sertraline in relation to genetic polymorphism of CYP2C19
AUTHOR(S): Wang, Jiu-Hui; Liu, Zhao-Qian; Wang, Wei; Chen, Xiao-Ping; Shu, Yan; He, Nan; Zhou, Hong-Hao
CORPORATE SOURCE: Pharmacogenetics Research Institute, Hunan Medical University, Changsha, 410078, Peop. Rep. China
SOURCE: Clinical Pharmacology & Therapeutics (St. Louis, MO, United States) (2001), 70(1), 42-47
CODEN: CLPTAT; ISSN: 0009-9236
PUBLISHER: Mosby, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, Desmethylsertraline
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(plasma concns. of desmethylsertraline in humans in relation to genetic polymorphism of CYP2C19)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 22 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

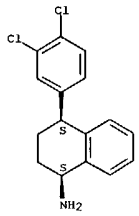
AB Recently, clin. depression has been identified as an independent risk factor for increased mortality in patients following acute coronary events. Although the underlying mechanisms of this link remain uncertain, increased platelet activity has been suggested but never proven as the mechanism responsible for this association Sertraline-HCl is a selective serotonin reuptake inhibitor (SSRI), and is an effective antidepressant agent. Its major liver metabolite, N-demethylsertraline (NDMS), is neurol. inactive. The in vitro effects of escalating concns. of sertraline and NDMS on human platelets were assessed in blood from healthy volunteers and patients with coronary artery disease by aggregometry in plasma and whole blood, by expression of major surface receptors with flow cytometry in washed cells and in the whole blood, and quant. by various platelet function analyzers. Pretreatment of blood samples with sertraline and NDMS resulted in a concentration-dependent inhibition of platelet-rich plasma aggregation induced by 5 μM ADP, by 10 μM ADP, by collagen, and by thrombin. Whole blood platelet aggregability was also reduced when induced by 20 μM ADP and by collagen. Surface expression of surface antigen CD9, glycoprotein (GP) Ib, GP IIb/IIIa, surface antigen VLA-2, P-selectin, and cell adhesion mol PECAM-1, but not the vitronectin receptor, was also reduced in sertraline- and NDMS-pretreated washed platelets. Whole-blood flow cytometry revealed inhibition of GP IIb/IIIa and P-selectin expression in NDMS-treated samples. Closure time was delayed for the collagen-ADP cartridge and for the collagen-epinephrine cartridge, indicating platelet inhibition in whole blood under high shear conditions. Rapid platelet-function assay revealed a decreased ability of platelets to agglutinate fibrinogen-coated beads, suggesting GP IIb/IIIa inhibition. Thus, both sertraline and its neurol. inactive metabolite, NDMS, exhibited significant concentration-dependent inhibition of human platelets. The antiplatelet effects of sertraline and NDMS may be directly related to the mortality benefits of SSRIs after ischemic events including myocardial infarction and stroke. (c) 2001 The Italian Pharmacological Society.

ACCESSION NUMBER: 2001:411281 CAPLUS
DOCUMENT NUMBER: 136:241479
TITLE: Platelet inhibition by sertraline and N-demethylsertraline: a possible missing link between depression, coronary events, and mortality benefits of selective serotonin reuptake inhibitors
AUTHOR(S): Serebruany, Victor L.; Gurbel, Paul A.; O'Connor, Christopher M.
CORPORATE SOURCE: Sinai Center for Thrombosis Research, Johns Hopkins University, Baltimore, MD, USA
SOURCE: Pharmacological Research (2001), 43(5), 453-461
CODEN: PHMREP; ISSN: 1043-6618
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, N-Demethylsertraline
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(platelet inhibition by sertraline and demethylsertraline as link between depression, coronary events, and mortality benefits of

L4 ANSWER 22 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
selective serotonin reuptake inhibitors in humans)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 23 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB The present invention pertains to methods for reducing the platelet activation state in an individual comprising administering a selective serotonin reuptake inhibitor (SSRI). The platelet activation state is reduced upon administering a SSRI, as measured by one or more platelet activation markers (PAMs). The invention also relates to methods for treating or preventing an individual at risk for a vascular event, disease
or disorder by administering a. For example, sertraline-HCl (Zoloft) had direct platelet inhibitory properties in humans. Moreover, N-desmethylsertraline, a stable final metabolite of sertraline which was previously considered inactive, exhibited potent dose-dependent effects inhibiting human platelets in both platelet rich plasma and in the whole blood.

ACCESSION NUMBER: 2000:824098 CAPLUS
DOCUMENT NUMBER: 134:522
TITLE: Methods of inhibiting platelet activation with selective serotonin reuptake inhibitors
INVENTOR(S): Serebruany, Victor L.; Gurbel, Paul A.; O'Connor, Christopher M.
PATENT ASSIGNEE(S): Heartdrug Research, L.L.C., USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

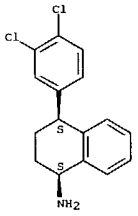
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000069429	A2	20001123	WO 2000-US13626	20000517
WO 2000069429	A3	20011004		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6245782	B1	20010612	US 1999-312987	19990517
CA 2375219	AA	20001123	CA 2000-2375219	20000517
EP 1183073	A2	20020306	EP 2000-932556	20000517
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AU 766904	B2	20031023	AU 2000-50258	20000517
ZA 2001009994	A	20020826	ZA 2001-9994	20011205

PRIORITY APPLN. INFO.: US 1999-312987 A1 19990517
WO 2000-US13626 W 20000517

IT **87857-41-8**, N-Demethylsertraline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)
(inhibition of platelet activation with selective serotonin reuptake inhibitors for treatment of cardiovascular disorders)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-

L4 ANSWER 23 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
(9CI) (CA INDEX NAME)

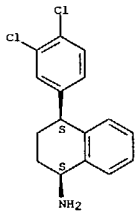
Absolute stereochemistry.



L4 ANSWER 24 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Three women were studied who were treated during pregnancy with fluvoxamine, sertraline, or venlafaxine. Amniotic fluid at amniocentesis and umbilical cord blood and maternal blood at delivery were collected and
analyzed for antidepressants and their metabolites by HPLC with UV detection. The antidepressants and their metabolites were detectable in all amniotic fluid samples studied, though concns. of the parent compound were less than those in maternal serum and umbilical cord blood. No adverse effects of the drugs were reported. The presence of these antidepressants in amniotic fluid suggests that fetal exposure to these compds. is continual and may occur through a variety of paths, thus accounting for increased fetal exposure. These paths include circulatory via placental passage, gastrointestinal via fetal swallowing, and respiratory secondary to fetal lung absorption.

ACCESSION NUMBER: 2000:807096 CAPLUS
DOCUMENT NUMBER: 135:28591
TITLE: Amniotic fluid and umbilical cord blood concentrations
of antidepressants in three women
AUTHOR(S): Hostetter, A.; Ritchie, J. C.; Stowe, Z. N.
CORPORATE SOURCE: Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA
SOURCE: Biological Psychiatry (2000), 48(10), 1032-1034
CODEN: BIPCBF; ISSN: 0006-3223
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Demethylsertraline
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(amniotic fluid and umbilical cord blood concns. of fluvoxamine, sertraline, venlafaxine, and their metabolites in women)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

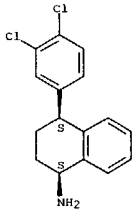
L4 ANSWER 24 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

L4 ANSWER 25 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB The in vitro biotransformation of bupropion to hydroxybupropion was studied in human liver microsomes and microsomes containing heterologously expressed human cytochromes P 450 (CYP). The mean (±S.E.) Km in four human liver microsomes was 89 (±14) μM. In microsomes containing cDNA-expressed CYPs, hydroxybupropion formation was mediated only by CYP2B6 at 50 μM bupropion (Km 85 μM). A CYP2B6 inhibitory antibody produced more than 95% inhibition of bupropion hydroxylation in four human livers. Bupropion hydroxylation activity at 250 μM was highly correlated with S-mephenytoin N-demethylation activity (yielding nirvanol), another CYP2B6-mediated reaction, in a panel of 32 human livers (r = 0.94). The CYP2B6 content of 12 human livers highly correlated with bupropion hydroxylation activity (r = 0.96). Thus bupropion hydroxylation is mediated almost exclusively by CYP2B6 and can serve as an index reaction reflecting activity of this isoform. IC50 values for inhibition of a CYP2D6 index reaction (dextromethorphan O-demethylation) by bupropion and hydroxybupropion were 58 and 74 μM, resp. This suggests a low inhibitory potency vs. CYP2D6, the clin. importance of which is not established. Since bupropion is frequently coadministered with other antidepressants, IC50 values (μM) for inhibition of bupropion hydroxylation were determined as follows: paroxetine (1.6), fluvoxamine (6.1), sertraline (3.2), desmethylsertraline (19.9), fluoxetine (59.5), norfluoxetine (4.2), and nefazodone (25.4). Bupropion hydroxylation was only weakly inhibited by venlafaxine, O-desmethylvenlafaxine, citalopram, and desmethylcitalopram. The inhibition of bupropion hydroxylation in vitro by a number of newer antidepressants suggests the potential for clin. drug interactions.

ACCESSION NUMBER: 2000:700645 CAPLUS
DOCUMENT NUMBER: 134:163
TITLE: CYP2B6 mediates the in vitro hydroxylation of bupropion: potential drug interactions with other antidepressants
AUTHOR(S): Hesse, Leah M.; Venkatakrishnan, Karthik; Court, Michael H.; Von Moltke, Lisa L.; Duan, Su X.; Shader, Richard I.; Greenblatt, David J.
CORPORATE SOURCE: Department of Pharmacology and Experimental Therapeutics, New England Medical Center, Tufts University School of Medicine, Boston, MA, 02111, USA
SOURCE: Drug Metabolism and Disposition (2000), 28(10), 1176-1183
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(CYP2B6 mediates in vitro hydroxylation of bupropion: potential drug interactions with other antidepressants)

L4 ANSWER 25 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



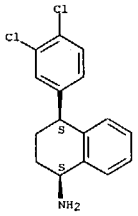
REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 26 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Formaldehyde is liberated in the process of cytochrome P 450 (CYP) mediated demethylation of a wide variety of compds. containing the CH3N or CH3O functionality. A highly sensitive method using a high-performance liquid chromatog. (HPLC) system with postcolumn derivatization was developed to measure the liberated formaldehyde as N- and O-demethylase activity of drugs in human liver microsomes. Following the chromatog. separation of formaldehyde on a C18 column, the formaldehyde was reacted with the Nash reagent in the postcolumn reactor at 100° and detected by the fluorescence method. The results showed that the present method has excellent precision and accuracy. The intra- and interassay variances of this method were less than 10%. The newly developed HPLC method was found to be about 80-fold more sensitive than the colorimetric method in detection of formaldehyde. The N-demethylase activity of sertraline in rat liver microsomes determined by the present method did not differ from those detected by previous methods quantifying produced desmethyl metabolite. The present method has been successfully applied to determine the N-demethylase activities of several drugs, including aminopyrine, erythromycin, fluoxetine, S-mephenytoin, and sertraline, in human liver microsomes. This assay should be useful for generic anal. of N- and O-demethylase activities of xenobiotic and endobiotic chems. by CYP enzymes. (c) 2000 Academic Press.

ACCESSION NUMBER: 2000:605323 CAPLUS
DOCUMENT NUMBER: 133:358817
TITLE: High-performance liquid chromatography determination of N- and O-demethylase activities of chemicals in human liver microsomes: application of postcolumn fluorescence derivatization using Nash reagent
AUTHOR(S): Kobayashi, Kaoru; Yamamoto, Tessai; Taguchi, Miwo; Chiba, Kan
CORPORATE SOURCE: Department of Biochemical Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Chiba University, Yayoi-cho, Chiba, 263-8522, Japan
SOURCE: Analytical Biochemistry (2000), 284(2), 342-347
CODEN: ANBCA2; ISSN: 0003-2697
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**
RL: ANT (Analyte); ANST (Analytical study)
(HPLC determination of N- and O-demethylase activities of chems. in human liver microsomes: postcolumn fluorescence derivatization using Nash reagent)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 26 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

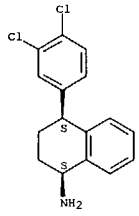


REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 27 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB This report describes sertraline pharmacokinetics derived from routine therapeutic drug monitoring (TDM) data. A high-performance liquid chromatog. method with UV detection was established for routine sertraline
TDM, and 924 analyses were performed from Apr. 1995 to May 1997. Extensive predefined inclusion/exclusion criteria were applied to increase
the validity of scientifically evaluated data. Subsequently, 605 samples (65.5%) were excluded. The remaining 319 samples from 319 patients, representative of steady state trough specimens and accompanied by essential clin. information provided on request forms, were scrutinized. A pronounced interindividual variability was observed Smokers had significantly lower concentration-to-dose (C/D) mean ratios of serum sertraline
(s-sert) and its main metabolite desmethylsertraline (s-dsert) than nonsmokers. Higher s-sert and s-dsert C/D mean ratios were found in elderly patients than in adults aged less than 65 yr. In a subset of 20 patients in whom repeated TDM analyses were performed, observed intraindividual sertraline TDM outcome variability was low. The results highlight sertraline TDM as a tool for individual dose optimization and evaluation of patient drug compliance as well as drug-drug interactions.
ACCESSION NUMBER: 2000:601711 CAPLUS
DOCUMENT NUMBER: 134:110069
TITLE: Therapeutic drug monitoring of sertraline: variability
factors as displayed in a clinical setting
AUTHOR(S): Lundmark, Jons; Reis, Margareta; Bengtsson, Finn
CORPORATE SOURCE: Department of Neuroscience and Locomotion, Division of
Psychiatry, Linkoping University Hospital, Linkoping, Swed.
SOURCE: Therapeutic Drug Monitoring (2000), 22(4), 446-454
CODEN: TDMODV; ISSN: 0163-4356
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, DESMETHYLSERTRALINE
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(therapeutic drug monitoring of sertraline)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 27 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

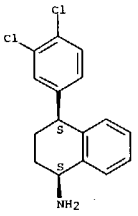


REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 28 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Propafenone is mainly metabolized by CYP2D6 to form 5-hydroxypropafenone (5-OHP) and to a minor extent by CYP1A2 and CYP3A4 to form N-depropylpropafenone (N-DPP). The in vitro inhibitory effect of selective serotonin reuptake inhibitors (SSRIs) on the formation of both metabolites was studied, using human liver microsomes. The 5-OHP formation from racemic propafenone and from its individual enantiomers followed 1-enzyme Michaelis-Menten kinetics. Incubation with the racemate
yielded a mean Vmax of 64 pmol · min-1 · mg-1 and a mean Km of 0.12 μm (N = 3). Stereoselectivity in Vmax and Km values was observed,
with (S)-propafenone displaying higher Km and Vmax values. N-DPP formation from racemic propafenone followed 1-enzyme Michaelis-Menten kinetics and yielded a mean Vmax of 403 pmol · min-1 · mg-1 and a mean Km of 116 μM (N=3). No stereoselectivity in propafenone N-dealkylation was observed The influence of SSRIs and quinidine, a prototypical CYP2D6 inhibitor, on propafenone 5-hydroxylation was investigated. Quinidine was the most potent inhibitor, followed by fluoxetine, norfluoxetine, and paroxetine. Sertraline, desmethylsertraline, and fluvoxamine had only a moderate inhibitory effect, whereas citalopram displayed slight or no inhibition when racemic propafenone was used as substrate. Mean Ki values of quinidine, fluoxetine, norfluoxetine, and paroxetine were 0.13, 0.33, 0.55, and 0.54 μM, resp. (N=3). Quinidine and paroxetine were also tested as inhibitors using the individual enantiomers, but no stereoselectivity was observed Among the SSRIs tested, only fluvoxamine substantially inhibited
propafenone N-dealkylation with a mean IC50 of 7.0 μM (N=3). There was a more pronounced inhibitory effect of fluvoxamine on (R)-propafenone than
on (S)-propafenone N-dealkylation. In conclusion, these in vitro data suggest that an in vivo interaction between propafenone and the SSRIs, fluoxetine and paroxetine, can be expected, which can lead to clin. relevant β-blockade and an increased risk of side effects in the central nervous system. An interaction with fluvoxamine may be of importance in poor metabolizers for CYP2D6.
ACCESSION NUMBER: 2000:558561 CAPLUS
DOCUMENT NUMBER: 134:95087
TITLE: Effect of selective serotonin reuptake inhibitors on the oxidative metabolism of propafenone. In vitro studies using human liver microsomes
AUTHOR(S): Hemeryck, Alex; De Vriendt, Cindy; Belpaire, Frans M.
CORPORATE SOURCE: Heymans Institute of Pharmacology, Ghent University Medical School, Ghent, 9000, Belg.
SOURCE: Journal of Clinical Psychopharmacology (2000), 20(4), 428-434
CODEN: JCPYDR; ISSN: 0271-0749
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(propafenone oxidative metabolism influenced by selective serotonin reuptake inhibitors and possible adverse drug interaction)
RN 87857-41-8 CAPLUS

L4 ANSWER 28 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

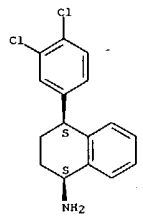


REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 29 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB This paper describes a set of simple and sensitive multiresidue methods for the determination of the specific serotonin reuptake inhibitors (SSRIs) used as antidepressant drugs, and some of their resp. active metabolites in human serum. It involves liquid-liquid extraction procedures followed by gas chromatog. coupled to nitrogen phosphorus detection or isocratic reversed-phase high-performance liquid chromatog. combined with fluorescence detection (HPLC-FL), depending on the analytes. Extraction recoveries were between 71 and 96% for the eight SSRIs and their metabolites analyzed by GC and between 41 and 77% for the two of them analyzed by HPLC. Limits of detection (LODs) and limits of quantitation (LOQs) ranged, resp., from 2.5 to 5 μg/l and from 10 to 20 μg/l. Intra-assay and inter-assay precision was studied at three and four concentration levels, resp., and was less than 19% for all compds. Accuracy was also satisfactory for all. An excellent linearity was observed from the LOQs up to 1000 μg/l for milnacipram and paroxetine and from each LOQ up to 400 mg/l for the other compds. The performance of the methods described thus allows the therapeutic drug monitoring of the currently commercialized SSRIs.
ACCESSION NUMBER: 2000:377581 CAPLUS
DOCUMENT NUMBER: 133:159587
TITLE: Methods for the determination of seven selective serotonin reuptake inhibitors and three active metabolites in human serum using high-performance liquid chromatography and gas chromatography
AUTHOR(S): Lacassie, E.; Gaulier, J.-M.; Marquet, P.; Rabatel, J.-F.; Lachatre, G.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, University Hospital, Limoges, 87042, Fr.
SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (2000), 742(2), 229-238
CODEN: JCBBEP; ISSN: 0378-4347
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods for determination of seven selective serotonin reuptake inhibitors and three active metabolites in human serum using high-performance liquid chromatog. and gas chromatog.)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 29 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

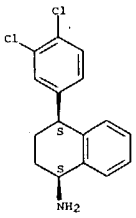


REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 30 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Grapefruit juice is an inhibitor of cytochrome P 450 3A4 (CYP3A4). This study assessed the in vitro and in vivo effects of grapefruit juice on sertraline metabolism The in vitro assay involved anal. of sertraline metabolism by CYP3A4, using CYP3A4-expressed human β-lymphoblast microsomes. The in vivo study involved HPLC anal. of serum trough levels of sertraline and demethylsertraline in patients who had been taking their usual dose of sertraline for ≥6 wk, followed by concurrent use of sertraline with grapefruit juice for 1 wk. The in vitro assay demonstrated that grapefruit juice concentration-dependently inhibited the formation of demethylsertraline. In the in vivo study, mean serum sertraline levels were determined in patients with a history of depression. The mean sertraline dosage was 55 mg/day. The results of the in vivo study appeared to be consistent with the in vitro findings, in that mean serum sertraline trough levels increased from 13.7 μg/L before to 20.2 μg/L after administration of grapefruit juice. Thus, the in vitro study demonstrated that grapefruit juice can inhibit the metabolism of sertraline.
ACCESSION NUMBER: 2000:29522 CAPLUS
DOCUMENT NUMBER: 132:58738
TITLE: The effects of grapefruit juice on sertraline metabolism: an in vitro and in vivo study
AUTHOR(S): Lee, Audrey J.; Chan, William K.; Harralson, Arthur F.; Buffum, John; Bui, Bao-Chau Crystal
CORPORATE SOURCE: School of Pharmacy and Health Sciences, University of the Pacific, Stockton, CA, USA
SOURCE: Clinical Therapeutics (1999), 21(11), 1890-1899
CODEN: CLTHDG; ISSN: 0149-2918
PUBLISHER: Excerpta Medica, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Demethylsertraline
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(grapefruit juice interaction with sertraline metabolism in humans as determined by formation of)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 30 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

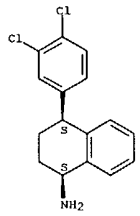


REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 31 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Aims: The present study was designed to define the kinetic behavior of sertraline N-demethylation in human liver microsomes and to identify the isoforms of cytochrome P 450 involved in this metabolic pathway.
Methods:
The kinetics of the formation of N-demethylsertraline were determined in human
liver microsomes from six genotyped CYP2C19 extensive (EM) and three poor metabolizers (PM). Selective inhibitors of and specific monoclonal antibodies to various cytochrome P 450 isoforms were also employed. Results: The kinetics of N-demethylsertraline formation in all EM liver microsomes were fitted by a two-enzyme Michaelis-Menten equation, whereas the kinetics in all PM liver microsomes were best described by a single-enzyme Michaelis-Menten equation similar to the low-affinity component found in EM microsomes. Mean apparent Km values for the high-and low-affinity components were 1.9 and 88 μM and Vmax values were 33 and 554 pmol min-1 mg-1 protein, resp., in the EM liver microsomes. Omeprazole (a CYP2C19 substrate) at high concns. and sulfaphenazole (a selective inhibitor of CYP2C9) substantially inhibited N-demethylsertraline formation. Of five monoclonal antibodies to various cytochrome P 450 forms tested, only anti-CYP2C8/9/19 had any inhibitory effect on this reaction. The inhibition of sertraline N-demethylation by anti-CYP2C8/9/19 was greater in EM livers than in PM livers at both low and high substrate concns. However, anti-CYP2C8/9/19 did not abolish the formation of N-demethylsertraline in the microsomes from any of the livers. Conclusions: The polymorphic enzyme CYP2C19 catalyzes the high-affinity N-demethylation of sertraline, while CYP2C9 is one of the low-affinity components of this metabolic pathway.
ACCESSION NUMBER: 1999:653227 CAPLUS
DOCUMENT NUMBER: 132:131735
TITLE: Evidence for involvement of polymorphic CYP2C19 and 2C9 in the N-demethylation of sertraline in human liver microsomes
AUTHOR(S): Xu, Zhen-Hua; Wang, Wei; Zhao, Xue-Jun; Huang, Song-Lin; Zhu, Bing; He, Nan; Shu, Yan; Liu, Zhao-Qian; Zhou, Hong-Hao
CORPORATE SOURCE: Pharmacogenetics Research Institute, Hunan Medical University, Changsha, 410078, Peop. Rep. China
SOURCE: British Journal of Clinical Pharmacology (1999), 48(3), 416-423
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, N-Demethylsertraline
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(evidence for involvement of polymorphic CYP2C19 and 2C9 in the N-demethylation of sertraline in human liver microsomes)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 31 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

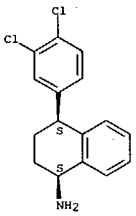


REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 32 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Three- and four-dimensional quant. structure activity relationship (3D/4D-QSAR) pharmacophore models of competitive inhibitors of CYP2D6 were
constructed using data from our laboratory or the literature. The 3D-QSAR
pharmacophore models of the common structural features of CYP2D6 inhibitors were built using the program Catalyst (Mol. Simulations, San Diego, CA, USA). These 3D-QSAR models were compared with 3D and 4D-QSAR partial least squares (PLS) models which were constructed using mol. surface-weighted holistic invariant mol. (MS-WHIM) descriptors of size and
shape of inhibitors. The first Catalyst model was generated from multiple
conformers of competitive inhibitors (n = 20) of CYP2D6 mediated bufurolol
1'-hydroxylation. This model demonstrated a correlation of observed and predicted Ki (apparent) values of r = 0.75. A second Catalyst model was constructed from literature derived Ki (apparent) values (n = 31) for the inhibition of CYP2D6. This model provided a correlation of observed and predicted inhibition for CYP2D6 of r = 0.91. Both Catalyst Ki pharmacophores were then validated by predicting the Ki (apparent) of a test set of known CYP2D6 inhibitors (n = 15). Ten out of 15 of these Ki (apparent) values were predicted to be within one log residual of the observed value using our CYP2D6 inhibitor model, while the literature model
predicted nine out of 15 values. Similarly, 3D- and 4D-QSARs derived from
PLS MS-WHIM for our dataset yielded predictable models as assessed using cross-validation. The corresponding cross-validated PLS MS-WHIM model for
the literature dataset yielded a comparable 3D-QSAR and improved 4D-QSAR value. Such computational models will aid in future prediction of drug-drug interactions.
ACCESSION NUMBER: 1999:635012 CAPLUS
DOCUMENT NUMBER: 132:146140
TITLE: Three and four dimensional-quantitative structure activity relationship (3D/4D-QSAR) analyses of CYP2D6 inhibitors
AUTHOR(S): Ekins, Sean; Bravi, Gianpaolo; Binkley, Shelly; Gillespie, Jennifer S.; Ring, Barbara J.; Wikel, James
H.; Wrighton, Steven A.
CORPORATE SOURCE: Departments of Drug Disposition, Lilly Research Laboratories, Eli Lilly and Co., Lilly Corporate Center, Indianapolis, IN, 46285, USA
SOURCE: Pharmacogenetics (1999), 9(4), 477-489
CODEN: PHMCEE; ISSN: 0960-314X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(3D/4D-QSAR analyses of CYP2D6 inhibitors)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-

L4 ANSWER 32 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
(9CI) (CA INDEX NAME)

Absolute stereochemistry.

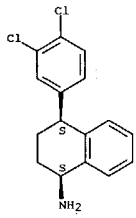


REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 33 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Sertraline, a new antidepressant of the selective serotonin re-uptake inhibitor class, is extensively metabolized to desmethylsertraline in humans. We identified the cytochrome P 450 (CYP) isoforms involved in sertraline N-demethylation using pooled human liver microsomes and cDNA-expressed CYP isoforms. Eadie-Hofstee plots for the sertraline N-demethylation in human liver microsomes were monophasic. The estimated Michaelis-Menten kinetic parameters were: KM = 18.1 ± 2.0 μM, Vmax = 0.45 ± 0.03 nmol/min/mg of protein, and Vmax/KM = 25.2 ± 4.3 μl/min/mg of protein. At the substrate concentration of 20 μM, which approximated the apparent KM value, sulfaphenazole (CYP2C9 inhibitor) and triazolam (CYP3A substrate) reduced the N-demethylation activities by 20 to 35% in human liver microsomes, whereas the inhibition induced by mephenytoin (CYP2C19 substrate) or quinidine (CYP2D6 inhibitor) was marginal. The anti-CYP2B6 antibody inhibited the sertraline N-demethylation activities by 35%. Sertraline N-demethylation activities were detected in all cDNA-expressed CYP isoforms studied. In particular, CYP2C19, CYP2B6, CYP2C9-Arg, CYP2D6-Val, and CYP3A4 all showed relatively high activity. When the contributions of CYP2D6, CYP2C9, CYP2B6, CYP2C19, and CYP3A4 were estimated from the Vmax/KM of cDNA-expressed CYP isoforms and from their contents in pooled human liver microsomes, the values were found to be 35, 29, 14, 13, and 9%, resp. The results suggest that at least five isoforms of CYP (CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP3A4) are involved in the sertraline N-demethylation in human liver microsomes and that the contribution of any individual isoform does not exceed 40% of overall metabolism Therefore, concurrent administration of a drug that inhibits a specific CYP isoform is unlikely to cause a marked increase in the plasma concentration of sertraline.
ACCESSION NUMBER: 1999:424018 CAPLUS
DOCUMENT NUMBER: 131:193674
TITLE: Sertraline N-demethylation is catalyzed by multiple isoforms of human cytochrome P-450 in vitro
AUTHOR(S): Kobayashi, Kaoru; Ishizuka, Tomoko; Shimada, Noriaki; Yoshimura, Yoshitaka; Kamijima, Kunitoshi; Chiba, Kan
CORPORATE SOURCE: Laboratory of Biochemical Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Chiba University, Chiba, 263-8522, Japan
SOURCE: Drug Metabolism and Disposition (1999), 27(7), 763-766
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(sertraline N-demethylation is catalyzed by multiple isoforms of human cytochrome P 450 in vitro)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 33 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

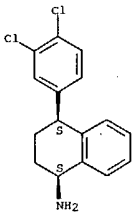


REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 34 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB This study was undertaken to determine whether there are pharmacokinetic (PK) interactions between zolpidem, a hypnotic, and sertraline, an antidepressant. Twenty-eight healthy female volunteers received a single dose of zolpidem alone and five consecutive dose(s) of zolpidem 10 mg in the presence of chronic doses (19 days) of sertraline 50 mg. Using HPLC, plasma levels of zolpidem, sertraline, and N-desmethylsertraline were determined at different times throughout the study and PK parameters derived. Compared to zolpidem alone, the T1/2 of the first dose of zolpidem in the presence of sertraline was reduced, the Cmax of the fifth zolpidem dose in the presence of sertraline was significantly increased, and its Tmax was significantly reduced. After five doses of zolpidem, the AUC of sertraline (-6%) and the Cmax of N-desmethylsertraline (+13%) were changed. There were no next-day effects of zolpidem on the Digit Symbol Substitution Test, and both drugs were well tolerated. Overall, coadministration of sertraline 50 mg and zolpidem 10 mg appears to be safe in healthy females but could result in a shortened onset of action and increased effect of zolpidem.
ACCESSION NUMBER: 1999:339280 CAPLUS
DOCUMENT NUMBER: 131:165239
TITLE: Coadministration of short-term zolpidem with sertraline in healthy women
AUTHOR(S): Allard, Stephane; Sainati, Stephen M.; Roth-Schechter, Barbara F.
CORPORATE SOURCE: Lorex Pharmaceuticals, Skokie, IL, 60680-5110, USA
SOURCE: Journal of Clinical Pharmacology (1999), 39(2), 184-191
CODEN: JCPCBR; ISSN: 0091-2700
PUBLISHER: Sage Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(drug interactions after coadministration of short-term zolpidem with sertraline in healthy women)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 34 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

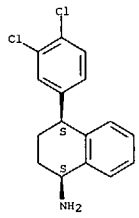


REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 35 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB The biotransformation of venlafaxine (VF) into its two major metabolites, O-desmethylvenlafaxine (ODV) and N-desmethylvenlafaxine (NDV) was studied in vitro with human liver microsomes and with microsomes containing individual
human cytochromes from cDNA-transfected human lymphoblastoid cells. VF was coincubated with selective cytochrome P 450 (CYP) inhibitors and several selective serotonin reuptake inhibitors (SSRIs) to assess their inhibitory effect on VF metabolism Formation rates for ODV incubated with
human microsomes were consistent with Michaelis-Menten kinetics for a single-enzyme mediated reaction with substrate inhibition. Mean parameters determined by non-linear regression were: Vmax = 0.36 nmol/min/mg
protein, Km = 41 μM, and Ks 22901 μM (Ks represents a constant which reflects the degree of substrate inhibition). Quinidine (QUI) was a potent inhibitor of ODV formation with a Ki of 0.04 μM, and paroxetine (PX) was the most potent SSRI at inhibiting ODV formation with a mean Ki value of 0.17 μM. Studies using expressed cytochromes showed that ODV was formed by CYP2C9, -2C19, and -2D6. CYP2D6 was dominant with the lowest Km, 23.2 μM, and highest intrinsic clearance (Vmax/Km ratio). No unique model was applicable to the formation of NDV for all four livers
tested. Parameters determined by applying a single-enzyme model were Vmax =
2.14 nmol/min/mg protein, and Km = 2504 μM. Ketoconazole was a potent inhibitor of NDV production, although its inhibitory activity was not as great
as observed with pure 3A substrates. NDV formation was also reduced by 42%
by a polyclonal rabbit antibody against rat liver CYP3A1. Studies using expressed cytochromes showed that NDV was formed by CYP2C9, -2C19, and -3A4. The highest intrinsic clearance was attributable to CYP2C19 and the
lowest to CYP3A4. However the high in vivo abundance of 3A isoforms will magnify the importance of this cytochrome. Fluvoxamine (FX), at a concentration
of 20 μM, decreased NDV production by 46% consistent with the capacity of
FX to inhibit CYP3A, 2C9, and 2C19. These results are consistent with previous studies that show CYP2D6 and -3A4 play important roles in the formation of ODV and NDV, resp. In addition the authors have shown that several other CYPs have important roles in the biotransformation of VF.
ACCESSION NUMBER: 1999:227255 CAPLUS
DOCUMENT NUMBER: 131:67604
TITLE: O- and N-demethylation of venlafaxine in vitro by human liver microsomes and by microsomes from cDNA-transfected cells: effect of metabolic inhibitors
and SSRI antidepressants
AUTHOR(S): Fogelman, Steven M.; Schmider, Jurgen; Venkatakrishnan, Karthik; Von Moltke, Lisa L.; Harmatz, Jerold S.; Shader, Richard I.; Greenblatt, David J.
CORPORATE SOURCE: Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, Boston, MA, 02111, USA
SOURCE: Neuropsychopharmacology (1999), 20(5), 480-490
CODEN: NEROEW; ISSN: 0893-133X
PUBLISHER: Elsevier Science Inc.

L4 ANSWER 35 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological
study, unclassified); BIOL (Biological study)
(O- and N-demethylation of venlafaxine in vitro by human liver microsomes and by microsomes from cDNA-transfected cells and role of cytochrome P 450 and effect of metabolic inhibitors and SSRI antidepressants)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

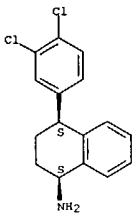


REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 36 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Objective: To investigate the in vitro potential of selective serotonin reuptake inhibitors (SSRIs) to inhibit two CYP2C9-catalyzed reactions, tolbutamide 4-methylhydroxylation and (S)-warfarin 7-hydroxylation. Methods: The formation of 4-hydroxytolbutamide from tolbutamide and that of 7-hydroxywarfarin from (S)-warfarin as a function of different concns. of SSRIs and some of their metabolites was studied in microsomes from three human livers. Results: Both tolbutamide 4-methylhydroxylation and (S)-warfarin 7-hydroxylation followed one enzyme Michaelis-Menten kinetics. Kinetic anal. of 4-hydroxytolbutamide formation yielded a mean apparent Michaelis-Menten constant (Km) of 133 μM and a mean apparent maximal velocity (Vmax) of 248 pmol·min-1·mg-1; formation of 7-hydroxywarfarin yielded a mean Km of 3.7 μM and a mean Vmax of 10.5 pmol·min-1· mg-1. Amongst the SSRIs and some of their metabolites tested, only fluvoxamine markedly inhibited both reactions. The average computed inhibition constant (Ki) values and ranges of fluvoxamine
when tolbutamide and (S)-warfarin were used as substrate, were 13.3 (6.4-17.3) μM and 13.0 (8.4-18.7) μM, resp. The average Ki value of fluoxetine for (S)-warfarin 7-hydroxylation was 87.0 (57.0-125) μM. Conclusion: Amongst the SSRIs tested, fluvoxamine was shown to be the most
potent inhibitor of both tolbutamide 4-methylhydroxylation and (S)-warfarin 7-hydroxylation. Fluoxetine, norfluoxetine, paroxetine, sertraline, desmethylsertraline, citalopram, desmethylcitalopram had little or no effect on CYP2C9 activity in vitro. This is consistent with in vivo data indicating that amongst the SSRIs, fluvoxamine has the greatest potential for inhibiting CYP2C9-mediated drug metabolism
ACCESSION NUMBER: 1999:116414 CAPLUS
DOCUMENT NUMBER: 131:39229
TITLE: Inhibition of CYP2C9 by selective serotonin reuptake inhibitors: in vitro studies with tolbutamide and (S)-warfarin using human liver microsomes
AUTHOR(S): Hemeryck, A.; De Vriendt, C.; Belpaire, F. M.
CORPORATE SOURCE: Heymans Institute of Pharmacology, University of Gent Medical School, Ghent, 9000, Belg.
SOURCE: European Journal of Clinical Pharmacology (1999), 54(12), 947-951
CODEN: EJCPAS; ISSN: 0031-6970
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(serotonin reuptake inhibitors inhibition of CYP2C9-mediated drug metabolism: tolbutamide and (S)-warfarin use as substrates in human liver
microsomes)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 36 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



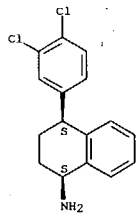
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 37 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB A 53-yr-old Caucasian male victim of suicide was suspected of overdose with sertraline and alprazolam after death-scene investigation. The concentration of sertraline, a selective serotonin reuptake inhibitor, was determined by a gas chromatograph with mass selective detection. The concentration of alprazolam, a triazolobenzodiazepine, was determined by high-performance liquid chromatog. The sertraline concentration was reported at 1.0 mg/L in peripheral blood, which is greater than previously reported in other postmortem cases in which death was attributed to a multiple drug overdose. The N-desmethylsertraline concentration was reported at 0.2 mg/L in peripheral blood, which is far less than in other postmortem cases and suggests acute intoxication in this case. The alprazolam concentration was reported at 33 μg/L in heart blood, which is within the therapeutic range. The cause of death was multiple drug intoxication following acute use of sertraline, the manner of death was suicide, and the mechanism of death is an unexplained drug interaction and/or toxicity.

ACCESSION NUMBER: 1998:664934 CAPLUS
DOCUMENT NUMBER: 130:21454
TITLE: Fatal multiple drug intoxication following acute sertraline use
AUTHOR(S): Milner, D. A.; Hall, M.; Davis, G. G.; Brisse, R: M.; Robinson, C. A.
CORPORATE SOURCE: Department of Pathology, Division of Forensic Pathology, University of Alabama at Birmingham, Birmingham, AL, USA
SOURCE: Journal of Analytical Toxicology (1998), 22(6), 545-548
CODEN: JATOD3; ISSN: 0146-4760
PUBLISHER: Preston Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, N-Demethylsertraline
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(fatal multiple drug intoxication in human following acute sertraline use)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 37 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 38 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB A veterinary method for clin. modifying the behavior of a household pet dog exhibiting a recognized type of canine affective aggression behavior is provided. The veterinary behavior modification method administers at least one compound selected from the group consisting of R enantiomers, S enantiomers, or a racemic mixture of selective serotonin reuptake inhibitors or their active metabolites to the dog upon one or multiple occasions; and the administration of these compds. will modify clin. the canine affective aggression behavior of the household dog permanently or for an indefinite period of time. This veterinary behavior modification method can be usefully employed as an adjunct to conditioning approaches presently employed and will avoid the need for euthanasia in extreme behavioral circumstances.

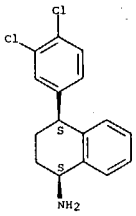
ACCESSION NUMBER: 1998:534794 CAPLUS
DOCUMENT NUMBER: 129:156948
TITLE: Modifying the behavior of dogs exhibiting canine affective aggression with R and S enantiomers or racemic mixtures of selective serotonin reuptake inhibitors or their metabolites
INVENTOR(S): Dodman, Nicholas H.
PATENT ASSIGNEE(S): Trustees of Tufts College, USA
SOURCE: U.S., 21 pp., Cont.-in-part of U.S. 5,554,383.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5788986	A	19980804	US 1996-699112	19960816
US 5554383	A	19960910	US 1995-417747	19950406
PRIORITY APPLN. INFO.:			US 1995-417747	19950406

IT **87857-41-8**, Desmethylsertraline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES
(Uses)
(modifying the behavior of aggressive dogs with R and S enantiomers or racemic mixts. of selective serotonin reuptake inhibitors or their metabolites)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 38 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

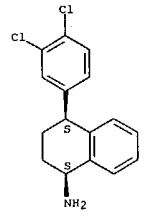


REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L4 ANSWER 39 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
sertraline, and their metabolites by gas chromatog.-mass spectrometry)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

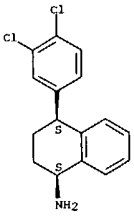
FORMAT

L4 ANSWER 39 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB A gas chromatog.-mass spectrometry method is presented which allows the simultaneous determination of the plasma concns. of the selective serotonin reuptake inhibitors citalopram, paroxetine, sertraline, and their pharmacol. active N-demethylated metabolites (desmethylcitalopram, didesmethylcitalopram, desmethylsertraline) after derivatization with the reagent N-methylbis(trifluoroacetamide). No interferences from endogenous compds. are observed following the extraction of plasma samples from six different human subjects. The standard curves are linear over a working range of 10-500 ng/mL for citalopram, 10-300 ng/mL for desmethylcitalopram, 5-60 ng/mL for didesmethylcitalopram, 20-400 ng/mL for sertraline and desmethylsertraline, and 10-200 ng/mL for paroxetine. Recoveries measured at three concns. range from 81 to 188% for the tertiary amines (citalopram and the interla standard methylmaprotiline), 73 to 95% for the secondary amines (desmethylcitalopram, paroxetine and sertraline), and 39 to 66% for the primary amines (didesmethylcitalopram and desmethylsertraline). Intra- and interday coeffs. of variation determined at three concns. range form 3 to 11% for citalopram and its metabolites, 4 to 15% for paroxetine, and 5 to 13% for sertraline and desmethylsertraline. The limits of quantitation of the method are 2 ng/mL for citalopram and paroxetine, 1 ng/mL for sertraline, and 0.5 ng/mL for desmethylcitalopram, didesmethylcitalopram, and desmethylsertraline. No interferences are noted from 20 other psychotropic drugs. This sensitive and specific method can be used for single-dose pharmacokinetics. It is also useful for therapeutic drug monitoring of these three drugs and could possibly be adapted for the quantitation of the two other selective serotonin reuptake inhibitors on the market, namely fluoxetine and fluvoxamine.
ACCESSION NUMBER: 1998:458150 CAPLUS
DOCUMENT NUMBER: 129:197500
TITLE: Simultaneous determination of human plasma levels of citalopram, paroxetine, sertraline, and their metabolites by gas chromatography-mass spectrometry
AUTHOR(S): Eap, C. B.; Bouchoux, G.; Amey, M.; Cochard, N.; Savary, L.; Baumann, P.
CORPORATE SOURCE: Unite de Biochimie et Psychopharmacologie Clinique, Departement Universitaire de Psychiatrie Adulte, Prilly-Lausanne, CH-1008, Switz.
SOURCE: Journal of Chromatographic Science (1998), 36(7), 365-371
CODEN: JCHSBZ; ISSN: 0021-9665
PUBLISHER: Preston Publications
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Demethylsertraline
RL: ANT (Analyte); BOC (Biological occurrence); BSU (Biological study, unclassified); MFM (Metabolic formation); ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(simultaneous determination of human plasma levels of citalopram, paroxetine,

L4 ANSWER 40 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB To characterize milk/plasma (M/P) ratio and infant exposure, for sertraline and N-desmethylsertraline, in breast-feeding women taking sertraline for the treatment of depression. Eight women (mean age 28 yr) taking sertraline (1.05 mg kg-1 day-1) and their infants (mean age 5.7 mo) were studied. Sertraline and N-desmethylsertraline in plasma and milk were measured by high-performance liquid chromatog. over a 24 h dose interval at steady-state. M/P values were estimated from area under the plasma and milk concentration-time curves. All milk produced was collected over the dose interval. Infant exposure was estimated as the product of actual or estimated milk production, and average drug concentration in milk, normalized to body weight and expressed as a percentage of the weight-adjusted maternal dose. Mean milk production was 321 mL day-1 (range 34-974 mL). Mean M/P values of 1.93 and 1.64 were calculated for sertraline and N-desmethylsertraline resp. Infant exposure estimated from actual milk produced was 0.2% and 0.3% of the weight-adjusted maternal dose for sertraline and N-desmethylsertraline (as sertraline equivalent) resp. When calculated from estimated milk production (0.15 l kg-1 day-1), infant exposure was significantly greater ($P<0.0001$) at 0.90% and 1.32% for sertraline and N-desmethylsertraline resp. Neither sertraline nor its N-desmethyl metabolite could be detected in plasma samples from the four infants tested. No adverse effects were observed in any of the eight infants and all had achieved normal developmental milestones. Irresp. of the method of calcn. of infant exposure, the mean total dose of sertraline and its N-desmethyl metabolite transmitted to infants via breast-feeding is low and unlikely to cause any significant adverse effects.
ACCESSION NUMBER: 1998:375347 CAPLUS
DOCUMENT NUMBER: 129:156408
TITLE: Distribution and excretion of sertraline and N-desmethylsertraline in human milk
AUTHOR(S): Kristensen, J. H.; Ilett, K. F.; Dusci, L. J.; Hackett, L. P.; Yapp, P.; Wojnar-Horton, R. E.; Roberts, M. J.; Paech, M.
CORPORATE SOURCE: Department of Pharmacy, King Edward Memorial and Princess Margaret Hospitals, Subiaco, 6008, Australia
SOURCE: British Journal of Clinical Pharmacology (1998), 45(5), 453-457
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(distribution and excretion of sertraline and N-desmethylsertraline in human milk)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

L4 ANSWER 40 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

Absolute stereochemistry.



REFERENCE COUNT: 23 THIS FORMAT THERE ARE 23 CITED REFERENCES AVAILABLE FOR RECORD. ALL CITATIONS AVAILABLE IN THE RE

L4 ANSWER 41 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB Objective: Biotransformation of metoprolol to α-hydroxymetoprolol (HM) and O-demethylmetoprolol (ODM) is mediated by CYP2D6. The selective serotonin reuptake inhibitors (SSRIs) are known to inhibit CYP2D6. The aim was to study in vitro the potential inhibitory effect of SSRIs on metoprolol biotransformation. Methods: Using microsomes from two human livers, biotransformation of metoprolol to α-hydroxymetoprolol (HM) and O-demethylmetoprolol (ODM) as a function of the concns. of the SSRIs and of some of their metabolites was studied. Results: The kinetics of the formation of both metabolites are best described by a biphasic enzyme model. The estimated values of Vmax and kM for the high affinity site are for the α-hydroxylation in human liver HL-1 32 pmol mg-1 min-1 and 75 μmol · l-1 resp., and in human liver HL-9 39 pmol mg-1 · min-1 and 70 μmol · l-1 resp.; for the O-demethylation in HL-1 131 pmol mg-1 min-1 and 95 μmol · l-1 resp., and in HL-9 145 pmol mg-1 min-1 and 94 μmol · l-1 resp. Quinidine is for both pathways a potent inhibitor of the high-affinity site, with Ki values ranging from 0.03 to 0.18 μmol · l-1. Fluoxetine, norfluoxetine and paroxetine are likewise potent inhibitors, with Ki values ranging from 0.30 to 2.1 μmol · l-1 fluvoxamine, sertraline, desmethylsertraline, citalopram and desmethylcitalopram are less potent inhibitors, with Ki values above 10 μmol · l-1. Conclusion: The rank order of the SSRIs for inhibition of metoprolol metabolism is comparable to that reported in the literature for other CYP2D6 substrates, with fluoxetine, norfluoxetine and paroxetine being the most potent. These findings need further investigation to determine their clin. relevance.

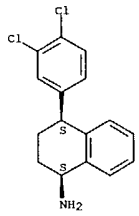
ACCESSION NUMBER: 1998:327690 CAPLUS
DOCUMENT NUMBER: 129:156445
TITLE: The oxidative metabolism of metoprolol in human liver microsomes: inhibition by the selective serotonin reuptake inhibitors
AUTHOR(S): Belpaire, F. M.; Wijnant, P.; Temmermann, A.; Rasmussen, B. B.; Brosen, K.
CORPORATE SOURCE: Heymans Institute of Pharmacology, University of Gent Medical School, De Pintelaan 185, Ghent, B-9000, Belg.
SOURCE: European Journal of Clinical Pharmacology (1998), 54(3), 261-264
CODEN: EJCPAS; ISSN: 0031-6970
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, Desmethylsertraline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(oxidative metabolism of metoprolol in human liver microsomes and inhibition by selective serotonin reuptake inhibitors)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 41 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 22 THIS FORMAT THERE ARE 22 CITED REFERENCES AVAILABLE FOR RECORD. ALL CITATIONS AVAILABLE IN THE RE

L4 ANSWER 42 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB The extent of changes in CYP2D6 and CYP1A2 activities with higher therapeutic dosages (>50 mg/day) of sertraline is not well established in vivo. This study assessed the extent and determinants of changes in CYP2D6 and CYP1A2 isoenzyme activities after treatment with clin. relevant doses of sertraline. Patients and healthy volunteers aged 19 to 85 yr (N = 21) were treated with sertraline for 5 to 55 days. The dosage of sertraline ranged from 25 to 150 mg/day (93.5 26.4 mg/day; mean ± SD). All subjects had an extensive metabolizer phenotype for CYP2D6 and received a single oral dose of dextromethorphan (30 mg) and caffeine (100 mg) before and after sertraline treatment. The log O-demethylation ratio (ODMR) of dextromethorphan and the caffeine metabolic ratio (CMR) in overnight urine were used as in vivo indexes of the CYP2D6 and CYP1A2 isoenzyme activities, resp. Concurrent medications and lifestyle habits (e.g., smoking and diet)-were monitored during the study. Baseline log ODMR (-2.33 ± 0.45) but not CMR (5.1 ± 1.9) (mean ± SD) significantly changed after sertraline treatment (-2.19 0.62; 4.5 ± 1.6, resp.) (p: ODMR = 0.04, CMR = 0.10). There was no significant effect of age, dose, duration of treatment, gender, sertraline and/or desmethylsertraline plasma concentration, subject type (patient or volunteer), and weight on the extent of changes in log ODMR or CMR (p > 0.05). In conclusion, sertraline treatment at a mean daily dosage of 94.0 mg did not significantly change CYP1A2 activity and resulted in a modest inhibition of CYP2D6 activity.

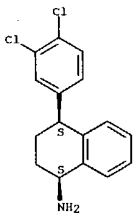
ACCESSION NUMBER: 1998:88540 CAPLUS
DOCUMENT NUMBER: 128:212643
TITLE: The extent and determinants of changes in CYP2D6 and CYP1A2 activities with therapeutic doses of sertraline
AUTHOR(S): Ozdemir, Vural; Naranjo, Claudio A.; Herrmann, Nathan; Shulman, Richard W.; Sellers, Edward M.; Reed, Ken; Kalow, Werner
CORPORATE SOURCE: Sunnybrook Health Science Centre, Women's College Hospital, Toronto, ON, Can.
SOURCE: Journal of Clinical Psychopharmacology (1998), 18(1), 55-61
CODEN: JCPYDR; ISSN: 0271-0749
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, Desmethylsertraline
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(sertraline effects on CYP2D6 and CYP1A2 activities in humans)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 42 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

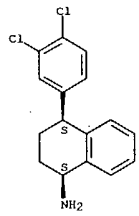


REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 43 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Several new antidepressants that inhibit the serotonin (SERT) and norepinephrine transporters (NET) have been introduced into clin. practice the past several years. This report focuses on the further pharmacol. characterization of nefazodone and its metabolites within the serotonergic and noradrenergic systems, in comparison with other antidepressants. By use of radioligand binding assays, we measured the affinity (Ki) of 13 antidepressants and 6 metabolites for the rat and human SERT and NET. The Ki values for eight of the antidepressants and three metabolites were also determined for the rat 5-HT1A, 5-HT2A and muscarinic cholinergic receptors, the guinea pig histaminel receptor and the human alpha-1 and alpha-2 receptors. These data are useful for predicting side effect profiles and the potential for pharmacodynamic drug-drug interactions of antidepressants. Of particular interest were the findings that paroxetine, generally thought of as a selective SERT antagonist, possesses moderately high affinity for the NET and that venlafaxine, which has been described as a "dual uptake inhibitor", possesses weak affinity for the NET. We observed significant correlations in SERT (r = 0.965) or NET (r = 0.983) affinity between rat and human transporters. Significant correlations were also observed between muscarinic cholinergic and NET affinity. There are several significant correlations between affinities for the 5-HT1A, 5-HT2A, histaminel, alpha-1 and alpha-2 receptors. These novel findings, not widely described previously, suggest that many of the, individual drugs studied in these expts. possess some structural characteristic that dets. affinity for several G protein-coupled, but not muscarinic, receptors.
ACCESSION NUMBER: 1998:26557 CAPLUS
DOCUMENT NUMBER: 128:162774
TITLE: Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites
AUTHOR(S): Owens, Michael J.; Morgan, W. Neal; Plott, Susan J.; Nemeroff, Charles B.
CORPORATE SOURCE: Laboratory of Neuropsychopharmacology, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1997), 283(3), 1305-1322
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(binding profile of antidepressants and their metabolites to serotonin and norepinephrine receptors and transporters)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 43 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS
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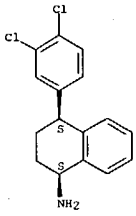
L4 ANSWER 44 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Using radioligand binding assays, we determined the equilibrium dissociation consts. (KD's) for 37 antidepressants, three of their metabolites (desmethylcitalopram, desmethylsertraline, and norfluoxetine), some mood stabilizers, and assorted other compds. (some antiepileptics, Ca2+ channel antagonists, benzodiazepines, psychostimulants, antihistamines, and monoamines) for the human serotonin, norepinephrine, and dopamine transporters. Among the compds. that we tested, mazindol was the most potent at the human norepinephrine and dopamine transporters with KD's of 0.45±0.03 nM and 8.1±0.4 nM, resp. Sertraline (KD=25±2 nM) and nomifensine (56±3 nM) were the two most potent antidepressants at the human dopamine transporter. We showed significant correlations for antidepressant affinities at binding to serotonin (R=0.93), norepinephrine (R=0.97), and dopamine (R=0.87) transporters in comparison to their resp. values for inhibiting uptake of monoamines into rat brain synaptosomes. These data are useful in predicting some possible adverse effects and drug-drug interactions of antidepressants and related compds.
ACCESSION NUMBER: 1997:808034 CAPLUS
DOCUMENT NUMBER: 128:149531
TITLE: Pharmacological profile of antidepressants and related compounds at human monoamine transporters
AUTHOR(S): Tatsumi, Masahiko; Groshan, Karen; Blakely, Randy D.; Richelson, Elliott
CORPORATE SOURCE: San Pablo Road, Mayo Clinic Jacksonville, Jacksonville, FL 32224, 4500, USA
SOURCE: European Journal of Pharmacology (1997), 340(2/3), 249-258
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmacol. profile of antidepressants and related compds. at human monoamine transporters)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 44 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
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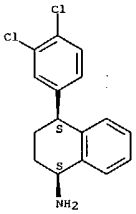
L4 ANSWER 45 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB A HPLC method for sertraline and desmethylsertraline determination in human plasma
and red blood cells is described.
ACCESSION NUMBER: 1997:779112 CAPLUS
DOCUMENT NUMBER: 128:70336
TITLE: Analysis of sertraline and desmethylsertraline in human plasma and red blood cells
AUTHOR(S): Vatassery, Govind T.; Holden, Lori A.; Hazel, Dana K.;
Dysken, Maurice W.
CORPORATE SOURCE: VA Medical Center, GRECC Program, Research Service, Minneapolis, MN, 55417, USA
SOURCE: Clinical Biochemistry (1997), 30(7), 565-568
CODEN: CLBIAS; ISSN: 0009-9120
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: ANT (Analyte); ANST (Analytical study)
(sertraline and desmethylsertraline determination in human plasma and red blood
cells by HPLC)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

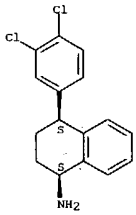


REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 46 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Inhibition of cytochrome P 450 (CYP) activity by selective serotonin reuptake inhibitors (SSRIs) has frequently been reported with regard to pathways mediated by CYP2D6, CYP3A4/5, and CYP1A2. Little data exist on the capability of SSRIs to inhibit CYP2C9. We investigated the effect of SSRIs on p-hydroxylation of phenytoin (PPH), an established index reaction
reflecting CYP2C9 activity, in an in vitro assay using liver tissue from six different human donors. In control incubations (without inhibitor), 5-(p-hydroxy-phenyl)-5-phenylhydantoin (HPPH) formation rates were: Vmax 0.023 nmol min-1 mg-1; Km 14.3 μM. Average inhibition consts. (Ki) differed significantly among the SSRIs, with fluvoxamine having the lowest
Ki (6 μM) followed by R-fluoxetine (13 μM), norfluoxetine (17 μM), RS-fluoxetine (19 μM), sertraline (33 μM), paroxetine (35 μM), S-fluoxetine (62 μM), and desmethylsertraline (66 μM). Thus, assuming comparable molar concns. at the site of inhibition, fluvoxamine can be expected to have the highest probability of interfering
with the metabolism of CYP2C9 substrates. S-fluoxetine is on average a 5 fold
weaker CYP2C9 inhibitor, than either R-fluoxetine or the racemic mixture These findings are consistent with published case reports describing SSRI-related increments in plasma phenytoin levels. Because phenytoin has
a narrow therapeutic index, plasma levels should be closely monitored when
SSRIs are coadministered.
ACCESSION NUMBER: 1997:752411 CAPLUS
DOCUMENT NUMBER: 128:84323
TITLE: Inhibition of CYP2C9 by selective serotonin reuptake inhibitors in vitro: studies of phenytoin p-hydroxylation
AUTHOR(S): Schmider, Jurgen; Greenblatt, David J.; Von Moltke, Lisa L.; Karsov, Dmitry; Shader, Richard I.
CORPORATE SOURCE: Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, Boston, MA, 02111, USA
SOURCE: British Journal of Clinical Pharmacology (1997), 44(5), 495-498
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(inhibition of CYP2C9 by selective serotonin reuptake inhibitors)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 46 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L4 ANSWER 47 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB Biotransformation of the H-1 antagonist terfenadine to its desalkyl and hydroxy metabolites was studied in vitro using microsomal prepns. of human liver. These metabolic reactions are presumed to be mediated by Cytochrome P 450-3A isoforms. The azole antifungal agent ketoconazole was a highly potent inhibitor of both reactions, having mean inhibition consts. (Ki) of 0.037 and 0.34 μM for desalkyl- and hydroxy-terfenadine formation, resp. Itraconazole also was a potent inhibitor, with Ki values of 0.28 and 2.05 μM, resp. Fluconazole, on the other hand, was a weak inhibitor. Six selective serotonin reuptake inhibitor antidepressants tested in this system were at least 20 times less potent inhibitors of terfenadine metabolism than was ketoconazole. An in vitro-in vivo scaling model used in vitro Ki values, typical clin. relevant plasma concns. of inhibitors, and presumed liver:plasmid partition ratios to predict the degree of terfenadine clearance impairment during coadministration of terfenadine with these inhibitors in humans. The model predicted a large and potentially hazardous impairment of terfenadine clearance by ketoconazole and, to a slightly lesser extent, by itraconazole. However, fluconazole and the six selective serotonin reuptake inhibitors (SSRIs) at usual clin. doses were not predicted to impair terfenadine clearance to a degree that would be of clin. importance. Caution is nonetheless warranted with the coadministration of SSRIs and terfenadine when high doses of SSRIs (particularly fluoxetine) are administered. Also, some individuals may be unusually susceptible to metabolic inhibition for a variety of reasons.

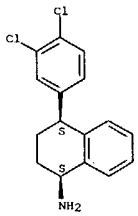
ACCESSION NUMBER: 1997:702816 CAPLUS
DOCUMENT NUMBER: 128:10069
TITLE: Inhibition of terfenadine metabolism in vitro by azole antifungal agents and by selective serotonin reuptake inhibitor antidepressants: relation to pharmacokinetic interactions in vivo
AUTHOR(S): von Moltke, Lisa L.; Greenblatt, David J.; Duan, Su Xiang; Harmatz, Jerold S.; Wright, Eugene C.; Shader, Richard I.
CORPORATE SOURCE: Dep. of Pharmacol. and Exp. Therapeutics, Div. of Clin. Pharmacol., New England med. Cent. Hosp., Tufts Univ. Sch. of Med., Boston, MA, 02111, USA
SOURCE: Journal of Clinical Psychopharmacology (1996), 16(2), 104-112
CODEN: JCPYDR; ISSN: 0271-0749
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, Desmethylsertraline
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(antifungal and antidepressants drugs interaction with terfenadine metabolism and pharmacokinetics)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 47 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 51 THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS FORMAT

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L4 ANSWER 48 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

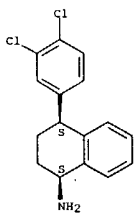
AB A HPLC method was developed for determination of risperidone and its therapeutically active main metabolite 9-hydroxyrisperidone in serum. After a single-step liquid-liquid extraction the analytes were separated on a C18 column and measured by UV detection at 280 nm. Inter-day coefficient of variation was <7% for both compds. at serum levels occurring in patients treated with ordinary doses. Studies of anal. interference showed that the most commonly coadministered antidepressants and benzodiazepines did not interfere. Some conventional low dose neuroleptics and clozapine did interfere, but this is of minor importance, because risperidone is intended as an alternative to these drugs.

ACCESSION NUMBER: 1997:573519 CAPLUS
DOCUMENT NUMBER: 127:272141
TITLE: Simplified high-performance liquid chromatographic method for determination of risperidone and 9-hydroxyrisperidone in serum from patients comedicated with other psychotropic drugs
AUTHOR(S): Olesen, Ole Vendelin; Linnet, Kristian
CORPORATE SOURCE: Institute for Basic Research in Psychiatry, Department of Biological Psychiatry, Clinical Biochemical Laboratory, Psychiatric Hospital, Aarhus University Hospital, Risskov, DK-8240, Den.
SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (1997), 698(1 + 2), 209-216
CODEN: JCBBEP; ISSN: 0378-4347
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, Demethylsertraline
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(HPLC assay for risperidone and 9-hydroxyrisperidone determination in serum from patients comedicated with other psychotropic drugs)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS

L4 ANSWER 48 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 49 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB A nonblinded study was conducted to compare the pharmacokinetic properties of the selective serotonin reuptake inhibitor sertraline in 22 young (aged 18 to 45 yr) and 22 elderly (> 65 yr) volunteers, of whom half were male and half were female. In this study, sertraline was administered at a dosage of 200mg once daily (the maximum recommended daily dosage) for 21 days after upward dosage titration from 50 mg/day over a 9-day period. Thus, this study was designed to measure the effect of age and gender on the pharmacokinetic properties of sertraline at the maximum dosage recommended for clin. use. The terminal elimination half-life (t1/2β) of sertraline was similar in young females, elderly males and elderly females (mean t1/2β ranged from 32.1 to 36.7 h in these groups) but shorter (22.4 h) in the young males. The mean maximum plasma sertraline concentration (Cmax) and the mean steady-state area under the plasma concentration-time curve from time zero to 24 h postdose (AUC24) were also similar between the young females, elderly males and elderly females, but were approx. 25% lower in the young males. The time to Cmax was unaffected by age or gender and ranged from 6.4 to 6.9 h. N-Demethylsertraline is the principal metabolite of sertraline and does not contribute significantly to its serotonergic actions. The mean values for N-demethylsertraline trough plasma concns., AUC24 and Cmax were comparable in elderly males and females and young females but lower in young males. The ratios of mean AUC24 and Cmax for N-demethylsertraline to the AUC24 and Cmax for sertraline were similar between the 4 groups.

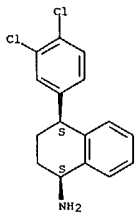
ACCESSION NUMBER: 1997:212626 CAPLUS
DOCUMENT NUMBER: 126:246336
TITLE: Pharmacokinetics of sertraline and its N-demethyl metabolite in elderly and young male and female volunteers
AUTHOR(S): Ronfeld, Robert A.; Tremaine, Larry M.; Wilner, Keith D.
CORPORATE SOURCE: Pfizer Central Research, Groton, CT, USA
SOURCE: Clinical Pharmacokinetics (1997), 32(Suppl. 1), 22-30
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, N-Demethylsertraline
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(pharmacokinetics of sertraline and its N-demethyl metabolite in elderly and young male and female volunteers)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 49 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L4 ANSWER 50 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

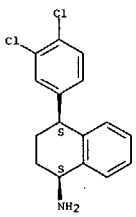
AB Initial expts. demonstrated that the original CEDIA (cloned enzyme donor immunoassay) benzodiazepine assay cross-reacted with sertraline and sertraline metabolites. In response to this phenomenon, Boehringer Mannheim Corporation developed an improved CEDIA benzodiazepine assay in order to eliminate sertraline cross-reactivity. The improved CEDIA assay was evaluated against the original CEDIA product, EMIT II (enzyme multiplied immunoassay technique) benzodiazepine assay and electron capture neg. chemical ionization (ECNCI) gas chromatog.-mass spectrometry (GC-MS). Five hundred and thirty-one urine drug screens were tested by the immunoassays. Sensitivity and specificity of these immunoassays for the 5-aryl-7-chloro-1,4-benzodiazepine compds. were 92 and 98%, resp., for the improved CEDIA assay; 92 and 93%, resp., for the current CEDIA assay; and 87 and 98%, resp., for EMIT II. The improved CEDIA assay performed almost identically to the EMIT II assay, both of which had a significant advantage over the origin CEDIA product, which was subject to cross-reactivity because of sertraline metabolites. The α-hydroxyketone metabolites of sertraline are identified in human urine specimens for the first time using ECNCI GC-MS.

ACCESSION NUMBER: 1997:77332 CAPLUS
DOCUMENT NUMBER: 126:196148
TITLE: Improved CEDIA benzodiazepine assay eliminates sertraline cross-reactivity
AUTHOR(S): Fitzgerald, Robert L.; Herold, David A.
CORPORATE SOURCE: Veterans Affairs Medical Center, Univ. California, San Diego, CA, 92161, USA
SOURCE: Journal of Analytical Toxicology (1997), 21(1), 32-35
CODEN: JATOD3; ISSN: 0146-4760
PUBLISHER: Preston Publications
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**
RL: ANT (Analyte); ANST (Analytical study)
(improved CEDIA benzodiazepine assay for elimination of sertraline cross-reactivity in human urine)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 50 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

L4 ANSWER 51 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB Biotransformation of phenacetin via O-de-ethylation to acetaminophen, an index reaction reflecting activity of Cytochrome P 450-1A2, was studied in microsomal prepns. from a series of human livers. Acetaminophen formation was consistent with a double Michaelis-Menten system, with low-Km (mean Km1 = 68 μM) and high-Km (mean Km2 = 7691 μM) components. The low-Km enzyme accounted for an average of 96% of estimated intrinsic clearance, and was predicted to contribute more than 50% of net reaction velocity at phenacetin concns. less than 2000 μM. Among index inhibitor probes, α-naphthotlavone was a highly potent inhibitor of the low-Km enzyme (Ki1 = 0.013 μM); furafylline also was a moderately active inhibitor (Ki1 = 4.4 μM), but its inhibiting potency was increased by preincubation with microsomes. Ketoconazole was a relatively weak inhibitor (Ki1 = 32 μM); quinidine and cimetidine showed minimal inhibiting activity. Among six selective serotonin reuptake inhibitor (SSRI) antidepressants, fluvoxamine was a potent inhibitor of 1A2 (mean Ki1 = 0.24 μM). The other SSRIs were more than ten-fold less potent. Mean Ki1 values were: floxetine, 4.4 μM; norfluoxetine, 15.9 μM; sertraline, 8.8 μM; desmethylsertraline, 9.5 μM; paroxetine, 5.5 μM. The antidepressant nefazodone and four of its metabolites (meta-chloro-phenylpiperazine, two hydroxylated derivs., and a triazoledione) were very weak inhibitors of P 450-1A2. Venlafaxine and its O- and N-desmethyl metabolites showed minimal inhibitory activity.

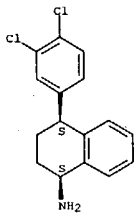
ACCESSION NUMBER: 1997:66943 CAPLUS
DOCUMENT NUMBER: 126:246342
TITLE: Phenacetin O-deethylation by human liver microsomes in vitro. Inhibition by chemical probes, SSRI antidepressants, nefazodone and venlafaxine
AUTHOR(S): Von Moltke, Lisa L.; Greenblatt, David J.; Duan, Su Xiang; Schmider, Juergen; Kudchadker, Leena; Fogelmann, Steven M.; Harmatz, Jerold S.; Shader, Richard I.
CORPORATE SOURCE: School Medicine, Tufts University, Boston, MA, 02111, USA
SOURCE: Psychopharmacology (Berlin) (1996), 128(4), 398-407
CODEN: PSCHDL; ISSN: 0033-3158
PUBLISHER: Springer
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, Desmethylsertraline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(phenacetin O-deethylation by human liver microsomes in vitro, inhibition by chemical probes, SSRI antidepressants, nefazodone, and venlafaxine)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 51 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L4 ANSWER 52 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB Substrates and inhibitors of the cytochrome P 450 isoenzyme CYP2D6 have overlapping structural characteristics. Two prototype serotonin uptake inhibitors, sertraline and fluoxetine, share these structural criteria and have been identified as potent inhibitors of CYP2D6 in vitro. The current study was undertaken to investigate whether genetically determined CYP2D6 activity alters the disposition of sertraline or fluoxetine or both. Single doses of sertraline (50 mg) and fluoxetine (20 mg) were administered successively to 20 young men with high (extensive metabolizers; n = 10) and low (poor metabolizers; n = 10) CYP2D6 activity. Blood and urine samples were collected for 5 to 7 half-lives and sertraline, desmethylsertraline, fluoxetine, and norfluoxetine were determined by GC and HPLC techniques. Poor metabolizers had significantly greater fluoxetine peak plasma concns. (Cmax; 57%), area under the concentration vs. time curve (AUC0-∞; 290%), and terminal elimination half-life (216%). compared with extensive metabolizers. The total amount of fluoxetine excreted in the urine during 8 days was almost three times higher in poor metabolizers than in extensive metabolizers (719 vs. 225 μg; $p < 0.05$), whereas the total amount of norfluoxetine excreted in urine of poor metabolizers was about half of that of extensive metabolizers (524 vs. 1047 μg; $p < 0.05$). Norfluoxetine Cmax and AUC0→t were significantly smaller in poor metabolizers (55% and 53%, resp.), and the partial metabolic clearance of fluoxetine into norfluoxetine was 10 times smaller in this group (4.3 ± 1.9 vs. 0.4 ± 0.1 L/h; $p < 0.05$). No significant differences between extensive and poor metabolizers were found for sertraline and desmethylsertraline pharmacokinetics. These data indicate that poor metabolizers accumulate fluoxetine but not sertraline and that CYP2D6 plays an important role in the demethylation of fluoxetine but not of sertraline.

ACCESSION NUMBER: 1997:8449 CAPLUS
DOCUMENT NUMBER: 126:42232
TITLE: The disposition of fluoxetine but not sertraline is altered in poor metabolizers of debrisoquin
AUTHOR(S): Hamelin, Bettina A.; Turgeon, Jacques; Vallee, Francois; Belanger, Pierre-Maxime; Paquet, Francois; LeBel, Marc
CORPORATE SOURCE: School of Pharmacy, the Quebec Heart Institute, Laval Hospital, and Anapharm Inc., Universite Laval, Sainte-Foy, QC, Can.
SOURCE: Clinical Pharmacology and Therapeutics (St. Louis) (1996), 60(5), 512-521
CODEN: CLPTAT; ISSN: 0009-9236
PUBLISHER: Mosby-Year Book
DOCUMENT TYPE: Journal
LANGUAGE: English

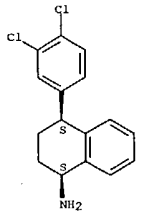
IT **87857-41-8**, Desmethylsertraline
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(disposition of fluoxetine but not sertraline is altered in poor metabolizers of debrisoquin)

RN 87857-41-8 CAPLUS

L4 ANSWER 52 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 53 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB This report introduces a flow-based extraction method where an aqueous sample and organic solvent are injected sequentially into an extraction coil, then mixed and separated due to the differential flow velocities of the aqueous and organic phases. A 500 µl aqueous sample is propelled through a 50 µl segment of organic solvent whose flow is impeded due to hydrophobic interactions with the walls of a Teflon extraction coil. This wall drag allows the faster moving aqueous sample to penetrate through and ultimately sep. from the slower organic solvent. These steps are repeated with a back extraction into a second aqueous segment (100µl) that is collected and analyzed with high-pressure liquid chromatog. (HPLC). The configuration of this novel sequential-injection extraction (SIE) system allows ease of changing reagents and uses min. organic solvent vols., as it avoids continuous pumping of reagents. Barbiturates (phenobarbital, amobarbital, pentobarbital and secobarbital) and serotonin re-uptake inhibitors (SRIs) - venlafaxine, paroxetine, sertraline and norsertraline - were extracted as model acidic and basic compds. from urine into a 1:4 (v:v) mixture of 1-octanol and Bu chloride and back extracted into 0.45M NaOH and 0.18M H3PO4, resp. Absolute recoveries of the analytes were: venlafaxine 29; paroxetine 30; norsertraline 25; sertraline 20; phenobarbital 11; amobarbital 24; pentobarbital 23; and secobarbital 27. The sample throughput, including extraction and back extraction, was 20 samples h-1.

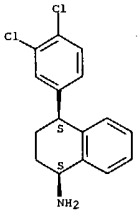
ACCESSION NUMBER: 1996:752602 CAPLUS
DOCUMENT NUMBER: 126:85763
TITLE: Sequential-injection extraction for sample preparation
AUTHOR(S): Peterson, Kristina L.; Logan, Barry K.; Christian, Gary D.; Ruzicka, Jaromir
CORPORATE SOURCE: University of Washington, Department of Chemistry, Box 351700, Seattle, WA, 98195-1700, USA
SOURCE: Analytica Chimica Acta (1997), 337(1), 99-106
CODEN: ACACAM; ISSN: 0003-2670
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8P**
RL: ANT (Analyte); PUR (Purification or recovery); ANST (Analytical study); PREP (Preparation)
(sequential-injection extraction for sample preparation)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 53 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L4 ANSWER 54 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB A simple method for the measurement of sertraline and norsertraline in plasma or serum suitable for use in single-dose pharmacokinetic studies has been developed. Internal standard solution, aqueous fenethazine (10 mg/L) (20 µL), and Tris buffer (2 mol/L, pH 10.6) (100 µL) were added to plasma (200 µL). Sertraline, norsertraline and the internal standard were extracted into Me tert-Bu ether (200 µL) by mixing (30 s) and centrifugation (11,000 r.p.m., 4 min). A portion (100 µL) of the extract was injected onto a Spherisorb S5SCX HPLC column (150 + 4.6 mm i.d.) which was eluted with methanol:water (19 + 1) containing ammonium perchlorate (40 mmol/L), final pH 7.0. Detection was by UV monitoring (215 nm). The concentration of each analyte in each sample was calculated from the calibration graph (peak-height ratio of analyte to that of the internal standard against analyte concentration) obtained after anal. of plasma samples containing known amts. of sertraline and norsertraline. The limit of accurate measurement of the assay was 10 µg/L sertraline and 20 µg/L norsertraline.

ACCESSION NUMBER: 1996:736563 CAPLUS
DOCUMENT NUMBER: 126:69664
TITLE: HPLC of sertraline and norsertraline in plasma or serum
AUTHOR(S): Patel, Jignasha; Spencer, E. P.; Flanagan, R. J.
CORPORATE SOURCE: Poisons Unit., St. Thomas' Hosp. Trust, London, SE14 5ER, UK
SOURCE: Biomedical Chromatography (1996), 10(6), 351-354
CODEN: BICHE2; ISSN: 0269-3879
PUBLISHER: Wiley
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **122873-19-2**, Norsertraline maleate
RL: ANT (Analyte); BSU (Biological study, unclassified); MFM (Metabolic formation); ANST (Analytical study); BIOL (Biological study); FORM (Formation, nonpreparative)
(sertraline and norsertraline determination in plasma or serum by HPLC)

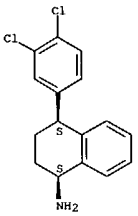
RN 122873-19-2 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 87857-41-8
CMF C16 H15 Cl2 N

Absolute stereochemistry.

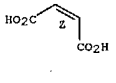
L4 ANSWER 54 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



CM 2

CRN 110-16-7
CMF C4 H4 O4

Double bond geometry as shown.



L4 ANSWER 55 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB Venlafaxine (V) is a second-generation antidepressant approved for use in the United States in 1993. It is a derivative of phenethylamine and is structurally unrelated to firs- and other second-generation antidepressants. Nevertheless, its mechanism of action is similar to other antidepressants; it inhibits the reuptake of presynaptic norepinephrine and serotonin. Its major routes of elimination involve O and N demethylation. O-Desmethylvenlafaxine (ODV) is biol. active. Therapeutic concns. of V and ODV are approx. 0.2 and 0.4 mg/L, resp. Three cases of drug intoxication involving V are presented. V and ODV were identified by gas chromatog.-nitrogen-phosphorus detection after alkaline extraction of the biol. specimen. On an HP-5 colum, V and ODV elute after bupropion and fluoxetine, but prior to the first-generation antidepressants, sertraline, amoxapine, and trazodone. V and ODV were confirmed by full scan electron impact gas chromatog.-mass spectrometry. The heart-blood V and ODV concns. (mg/L) in the three cases were 6.6 and 31; 84 and 15, and 44 and 50, resp. In case 1, acetaminophen and diphenhydramine were found in the heart blood at 140 and 2.6 mg/L resp. In case 2, amitriptyline, nortriptyline, and chlordiazepoxide were found in the blood at 2.8, 0.5 and 3.3 mg/L, resp. In each case, the manner of death was suicide.

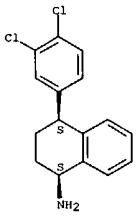
ACCESSION NUMBER: 1996:599888 CAPLUS
DOCUMENT NUMBER: 125:240430
TITLE: Distribution of venlafaxine in three postmortem cases
AUTHOR(S): Levine, Barry; Jenkins, Amanda J.; Queen, Martin; Jufer, Rebecca; Smialek, John E.
CORPORATE SOURCE: Office Chief Medical Examiner, Baltimore, MD, 21201, USA
SOURCE: Journal of Analytical Toxicology (1996), 20(6), 502-505
CODEN: JATOD3; ISSN: 0146-4760
PUBLISHER: Preston Publications
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, Desmethylsertraline
RL: ANT (Analyte); ANST (Analytical study)
(venlafaxine in three postmortem cases)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 55 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L4 ANSWER 56 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB N-demethylation of the selective serotonin reuptake inhibitor sertraline to desmethylsertraline yields a compound with 10- to 20-fold less potency at blocking serotonin (5-HT) reuptake as measured in vitro. In the present study desmethylsertraline (DMS) was examined in two in vivo models of reuptake inhibition-elevation of extracellular 5-HT in the corpus striatum as measured by microdialysis and inhibition of firing of serotonin-containing dorsal raphe neurons. Whereas sertraline (1, 3.2, and 10 mg/kg SC) produced a dose-dependent increase in extracellular 5-HT and a decrease in 5-HIAA in rat striatum, desmethylsertraline was without effect on either parameter. In similar fashion, desmethylsertraline had no effect on dorsal raphe cell firing at a dose (1,000 μg/kg IV) nearly 20-fold the ED50 for sertraline (52 μg/kg). Taken together, these data suggest that DMS does not contribute to the blockade of central 5-HT reuptake produced by sertraline in vivo and therefore would be expected to play a negligible role in its clin. activity.

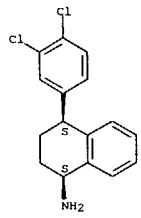
ACCESSION NUMBER: 1996:239456 CAPLUS
DOCUMENT NUMBER: 124:332755
TITLE: Comparison of the effects of sertraline and its metabolite desmethylsertraline on blockade of central 5-HT reuptake in vivo
AUTHOR(S): Sprouse, Jeffrey; Clarke, Thomas; Reynolds, Linda; Heym, James; Rollema, Hans
CORPORATE SOURCE: Department Neuroscience, Pfizer Central Research, Groton, CT, 06340, USA
SOURCE: Neuropsychopharmacology (1996), 14(4), 225-31
CODEN: NEROEW; ISSN: 0893-133X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, Desmethylsertraline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)
(comparison of effects of sertraline and its metabolite desmethylsertraline on blockade of central 5-HT reuptake in vivo)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

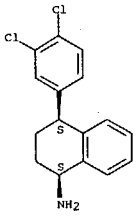
L4 ANSWER 56 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L4 ANSWER 57 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Biotransformation of the triazolobenzodiazepine triazolam to its hydroxylated metabolites, α-hydroxy (OH)- and 4-OH-triazolam, was studied in vitro using microsomal prepns. of human liver. Mean values of Vmax (10.3 nM/min/mg of protein) and Km (304 μM) for the 4-OH pathway exceeded values for the α-OH pathway (2.4 and 74, resp.). However, the mean Vmax/Km ratios for the two pathways were nearly identical, indicating that both contribute approx. equally to intrinsic clearance. Ketoconazole was a powerful inhibitor of triazolam biotransformation, having mean competitive Ki values of 0.006 and 0.023 μM for the α-OH and 4-OH pathways. This is consistent with the role of P 450-3A isoforms in mediating triazolam biotransformation. The serotonin2 antagonist antidepressant nefazodone inhibited the α-OH and 4-OH pathways (Ki = 0.6 and 1.7 μM, resp.), but with considerably less activity than ketoconazole. Among six selective serotonin reuptake-inhibitor antidepressants, norfluoxetine was the most potent inhibitor (Ki = 2.7 and 8.0 μM) and fluoxetine itself was the weakest (Ki = 7.0 and 44.3 μM). In a double-blind clin. pharmacokinetic-pharmacodynamic study, administration of triazolam (0.125 mg) preceded by ketoconazole, compared to triazolam preceded by placebo, produced a nearly 9-fold reduction in apparent oral clearance of triazolam (41 vs. 337 mL/min) and a 4-fold prolongation of half-life (13.5 vs. 3.4 h). Pharmacodynamic testing indicated enhancement of electroencephalog. beta activity, and enhanced decrements in digit-symbol substitution test performance, attributable to coadministration of ketoconazole. Plasma ketoconazole concns. measured in the clin. study ranged from 0.02 μg/mL (projected min.) to 4.95 μg/mL (maximum). An in vitro-in vivo scaling model, using these plasma ketoconazole concns. together with liver partition ratios and the in vitro Ki values, predicted with liver partition ratios and the in vitro ki values, predicted a decrement of triazolam clearance due to ketoconazole coadministration that was consistent with the 88% decrement in clearance activity observed in vivo.
ACCESSION NUMBER: 1996:112719 CAPLUS
DOCUMENT NUMBER: 124:219303
TITLE: Triazolam biotransformation by human liver microsomes in vitro: effects of metabolic inhibitors and clinical conformation of a predicted interaction with ketoconazole
AUTHOR(S): von Moltke, Lisa L.; Greenblatt, David J.; Harmatz, Jerold S.; Duan, Su Xiang; Harrel, Lisa M.; Cotreau-Bibbo, Monette M.; Pritchard, Gary A.; Wright, C. Eugene; Shader, Richard I.
CORPORATE SOURCE: Tufts University School of Medicine and The Division of Clinical Pharmacology, New England Medical Center, Boston, MA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1996), 276(2), 370-9
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)

L4 ANSWER 57 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
(metab. of triazolam and drug interactions)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

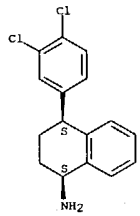
Absolute stereochemistry.



L4 ANSWER 58 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB Desmethylsertraline, a metabolite of the antidepressant drug sertraline, was compared with sertraline for its ability to produce effects characteristic of inhibitors of the serotonin transporter in vivo. Desmethylsertraline antagonized brain serotonin depletion by p-chloroamphetamine, a depletion dependent upon the serotonin transporter, being less potent than sertraline in rats but almost as potent as sertraline in mice. Desmethylsertraline was a weak antagonist of 6-hydroxydopamine-induced depletion of heart norepinephrine in mice; sertraline had no effect at the doses studied. Desmethylsertraline decreased brain concns. of 5-hydroxyindoleacetic acid (5HIAA) in rats as did sertraline, the duration of the effect after both drugs being at least 24 h but less than 48 h. After sertraline injection, desmethylsertraline was present in rat brain at higher concns. than the parent drug at 8 h and thereafter. In rats, repeated injections of sertraline, at doses previously shown to diminish β-adrenergic receptor-mediated responses, led to marked accumulation of desmethylsertraline in brain and to inhibition of the catecholamine transporters. In mice, brain concns. of desmethylsertraline were higher than those of parent drug within 7 h after sertraline injection and probably contributed importantly to the antagonism of p-chloroamphetamine effects. These data show that desmethylsertraline is less potent than sertraline as a serotonin uptake inhibitor in vivo, as the in vitro data would have predicted, but that desmethylsertraline may nonetheless contribute to the prolonged inhibition of the serotonin transporter after sertraline administration, perhaps more in mice than in rats.
ACCESSION NUMBER: 1995:387035 CAPLUS
DOCUMENT NUMBER: 122:178161
TITLE: Comparison of desmethylsertraline with sertraline as a monoamine uptake inhibitor in vivo
AUTHOR(S): Fuller, Ray W.; Hemrick-Luecke, Susan K.; Littlefield, Ethel S.; Audia, James E.
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA
SOURCE: Progress in Neuro-Psychopharmacology & Biological Psychiatry (1995), 19(1), 135-49
CODEN: PNPPD7; ISSN: 0278-5846
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(comparison of desmethylsertraline with sertraline as a monoamine uptake inhibitor in brain in vivo)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 58 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L4 ANSWER 59 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB The biotransformation of the triazolobenzodiazepine alprazolam (ALP) to its hydroxylated metabolites (4-OH-ALP and α-OH-ALP) was evaluated in human, monkey, rat, and mouse liver microsomes. In all species 4-OH-ALP was the principal metabolite, accounting for 84% of clearance in human microsomes compared with 16% for α-OH-ALP. Among the serotonin-specific reuptake inhibitors fluoxetine (FLU) and sertraline (SERT), and their resp. demethylated metabolites norfluoxetine (NOR) and desmethylsertraline (DES), NOR was the most potent inhibitor (mean Ki for 4-OH-ALP formation in humans: 11 μM), FLU the weakest (Ki = 83 μM), with SERT and DES falling in between (Ki = 24 and 20 μM). The in vitro data predict 29% inhibition of ALP clearance at mean FLU and NOR plasma concns. of 77 ng mL-1 and 72 ng mL-1, resp., after correction for liver:water partition ratios in the range of 12-14. The observed mean degree of inhibition in a previous in vivo study was 21%. Ketoconazole was a potent inhibitor of ALP metabolism in vitro (Ki = 0.046 μM), suggesting that ALP hydroxylation is mediated by the cytochrome P 450-3A subfamily. Quinidine was a weak inhibitor (Ki = 626 μM).

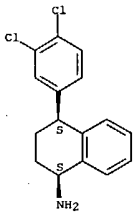
ACCESSION NUMBER: 1994:620997 CAPLUS
DOCUMENT NUMBER: 121:220997
TITLE: Inhibitors of alprazolam metabolism in vitro: Effect of serotonin-reuptake-inhibitor antidepressants, ketoconazole and quinidine
AUTHOR(S): Moltke, Lisa L. von; Greenblatt, David J.; Cotreau-Bibbo, Monette M.; Harmatz, Jerold S.; Shader, Richard I.
CORPORATE SOURCE: New England Medical Center Hospital, Tufts University School Medicine, Boston, MA, 02111, USA
SOURCE: British Journal of Clinical Pharmacology (1994), 38(1), 23-31
CODEN: BCPHBM; ISSN: 0306-5251
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, Desmethylsertraline
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(alprazolam metabolism inhibition by desmethylsertraline)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 59 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L4 ANSWER 60 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB Using radioligand binding assays and post-mortem normal human brain tissue, the authors obtained equilibrium dissociation consts. (Kds) for 17 antidepressants and two of their metabolites at histamine H1, muscarinic, α1-adrenergic, α2-adrenergic, dopamine D2, serotonin 5-HT1A, and serotonin 5-HT2 receptors. Several newer antidepressants were compared with older drugs. In addition, the authors studied some antimuscarinic, antiparkinson, antihistamine, and neuroleptic compds. at some of these receptors. For the antidepressants, classical tricyclic antidepressants were the most potent drugs at five of the seven receptors (all but α2-adrenergic and 5-HT1A receptors). The chlorophenylpiperazine derivative antidepressants (etoperidone, nefazodone, trazodone) were the most potent antidepressants at α2-adrenergic and 5-HT1A receptors. Of ten antihistamines tested, none was more potent than doxepin at histamine H1 receptors. At muscarinic receptors antidepressants and antihistamines had a range of potencies, which were mostly weaker than those for antimuscarinics. From the in vitro data, the authors expect adinazolam, bupropion, fluoxetine, sertraline, tomoxetine, and venlafaxine not to block any of these five receptors in vivo. An antidepressant's potency for blocking a specific receptor is predictive of certain side effects and drug-drug interactions. These studies can provide guidelines for the clinician in the choice of antidepressant.

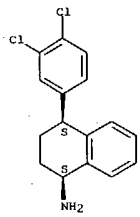
ACCESSION NUMBER: 1994:449972 CAPLUS
DOCUMENT NUMBER: 121:49972
TITLE: Binding of antidepressants to human brain receptors: focus on newer generation compounds
AUTHOR(S): Cusack, Bernadette; Nelson, Albert; Richelson, Elliott
CORPORATE SOURCE: Dep. Res., Mayo Clin. Jacksonville, Jacksonville, FL, 32224, USA
SOURCE: Psychopharmacology (Berlin, Germany) (1994), 114(4), 559-65
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, Desmethylsertraline
RL: PROC (Process)
(binding of, to human brain receptors)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 60 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L4 ANSWER 61 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

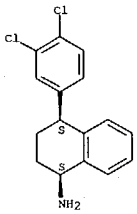
AB The authors report methods for the anal. of sertraline and desmethylsertraline in postmortem biol. fluids. The extraction method is based on a widely used procedure employing Bu chloride, and instrumental anal. is performed using GC/MS and HPLC with photodiode array detection. The authors report retention index, mass spectral, and UV-vis properties of the drug and its metabolite. Samples from three sertraline-related deaths were analyzed and revealed concns. up to 10 times greater than the normal therapeutic levels, although two of the deaths were obviously the result of other causes. The authors also noted in one case that the drug concns. in central and peripheral blood were very similar, suggesting that postmortem distribution may be uniform.

ACCESSION NUMBER: 1994:426134 CAPLUS
DOCUMENT NUMBER: 121:26134
TITLE: Analysis of sertraline (Zoloft) and its major metabolite in postmortem specimens by gas and liquid chromatography
AUTHOR(S): Logan, B. K.; Friel, P. N.; Case, G. A.
CORPORATE SOURCE: Dep. Lab. Med., Univ. Washington, Seattle, WA, 98134, USA
SOURCE: Journal of Analytical Toxicology (1994), 18(3), 139-42
CODEN: JATOD3; ISSN: 0146-4760
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, Desmethylsertraline
RL: ANT (Analyte); ANST (Analytical study)
(determination of, as sertraline metabolite, in postmortem human blood by gas and liquid chromatog.)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 62 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

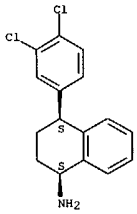
AB The determination of the new antidepressant drug sertraline and its main metabolite, desmethylsertraline, in human serum is described. A new solid-phase extraction method employing the dual functionality Clean Screen® cartridge is presented followed by reversed-phase liquid chromatog. (LC) anal. The sample preparation yielded extremely clean exts. and absolute recoveries in excess of 90% for both drugs from human serum. The response of the LC system was linear over the concentration range 0.01-2.5mg/L for both sertraline and desmethylsertraline with a limit of detection of 0.01mg/L. A gas chromatog.-mass spectrometric (GC-MS) system is also described should confirmation of the drugs be necessary.

ACCESSION NUMBER: 1994:289312 CAPLUS
DOCUMENT NUMBER: 120:289312
TITLE: Determination of sertraline and desmethylsertraline in human serum using copolymeric bonded-phase extraction, liquid chromatography and gas chromatography-mass spectrometry
AUTHOR(S): Rogowsky, Dawn; Marr, Margaret; Long, Gerald; Moore, Christine
CORPORATE SOURCE: United Chemical Technologies, 2731 Bartram Road, Bristol, PA, 19007, USA
SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (1994), 655(1), 138-41
CODEN: JCBBEP; ISSN: 1387-2273
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, Desmethylsertraline
RL: ANT (Analyte); ANST (Analytical study)
(determination of, in human blood by reversed-phase liquid chromatog. and gas chromatog.-mass spectrometry)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 62 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

L4 ANSWER 63 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB Biotransformation of the tricyclic antidepressant desipramine (DMI) to its metabolite 2-hydroxy-desipramine (2-OH-DMI) was studied in vitro using microsomal prepns. from human, monkey, mouse and rat liver. In all species 2-OH-DMI was the principal identified metabolite. Mean (±S.E.) reaction parameters in six human liver samples were: Vmax, 0.11 ± .02 nmol/mL/min/mg protein; Km, 16.1 ± 4.2 μM. Quinidine was a highly potent inhibitor of 2-OH-DMI formation (mean Kj = 0.053 μM), consistent with the presumed role of Cytochrome P 450-2D6 in mediating this reaction. Ketoconazole was a much less potent inhibitor (mean Ki = 10.3 μM). Two serotonin-specific reuptake inhibitor (SSRI) antidepressants, and their resp. metabolites, were evaluated as potential inhibitors of 2-OH-DMI formation. Fluoxetine (FLU) and norfluoxetine (NOR) were the most potent inhibitors (mean Ki values: 3.0 and 3.5 μM, resp.). Sertraline (SERT) and its metabolite desmethylsertraline (DES) also inhibited the reaction (mean Kj: 22.7 and 16.0 μM), but were significantly less potent than FLU or NOR. Values of Kj and Km measured in vitro were used to generate a theor. prediction of the degree of clearance inhibition in vivo at any given concentration of substrate and inhibitor. The model was applied to a clin. study in which DMI clearance in humans was impaired by coadministration of FLU (yielding FLU and NOR in plasma) or by SERT (yielding SERT and DES in plasma). Use of plasma SSRI concns. in the predictive model underestimated the actual impairment of DMI clearance. However, in vitro liver:water partition ratios for the SSRIs were in the range of 12 to 14, suggesting that liver concns. will considerably exceed those in plasma. Use of projected liver SSRI concns. (plasma level + partition ratio) in the model yielded highly accurate predictions. Predicted vs. observed impairments of DMI clearance were: 81.7 vs. 79.2% due to FLU/NOR; 17.5 vs. 16.7% due to SERT/DES. Thus, in vitro drug metabolism models can provide qual. and quant. data on drug interactions that are of direct clin. relevance.

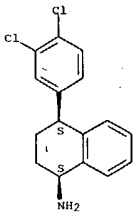
ACCESSION NUMBER: 1994:260419 CAPLUS
DOCUMENT NUMBER: 120:260419
TITLE: Inhibition of desipramine hydroxylation in vitro by serotonin-reuptake-inhibitor antidepressants, and by quinidine and ketoconazole: a model system to predict drug interactions in vivo
AUTHOR(S): Von Moltke, Lisa L.; Greenblatt, David J.; Cotreau-Bibbo, Monette M.; Duan, Su Xiang; Harmatz, Jerold S.; Shader, Richard I.
CORPORATE SOURCE: Sch. Med., Tufts Univ., Boston, MA, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1994), 268(3), 1278-83
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, Desmethylsertraline
RL: ANST (Analytical study)
(desipramine hydroxylation in liver microsome model inhibition by, drug interaction prediction in relation to)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

L4 ANSWER 63 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

Absolute stereochemistry.



L4 ANSWER 64 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB Paroxetine is a selective and potent inhibitor of 5-hydroxytryptamine (5-HT) uptake into serotonergic neurons. [3H]paroxetine binding to rat frontal cortex was of high affinity with a high percentage of sp. binding.

The binding data of both competition and saturation studies fitted a single site binding model. [3H]paroxetine binding was potently inhibited by the selective 5-HT uptake inhibitors. In addition, a very good correlation was demonstrated between the ability of twenty-three compds. to inhibit [3H]paroxetine binding to rat frontal cortical membranes and [3H]5-HT uptake into rat frontal cortical synaptosomes. These data support the view that [3H]paroxetine binds to a single site which corresponds to the 5-HT uptake site. Using this ligand, the effects of repeated administration of antidepressant drugs with a wide range of pharmacol. actions and electroconvulsive shock on 5-HT reuptake sites were examined [3H]paroxetine binding parameters (Kd and Bmax) were unaltered by all treatments. It would, therefore, appear that antidepressant therapy does not produce adaptive changes in 5-HT uptake sites.

ACCESSION NUMBER: 1993:595588 CAPLUS
DOCUMENT NUMBER: 119:195588
TITLE: [3H]Paroxetine binding in rat frontal cortex strongly correlates with [3H]5-HT uptake: effect of administration of various antidepressant treatments
AUTHOR(S): Cheetham, S. C.; Viggers, J. A.; Slater, N. A.; Heal, D. J.; Buckett, W. R.
CORPORATE SOURCE: Boots Pharm. Res. Dep., Nottingham, NG2 3AA, UK
SOURCE: Neuropharmacology (1993), 32(8), 737-43
CODEN: NEPHBW; ISSN: 0028-3908
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **122873-19-2**, Desmethylsertraline maleate
RL: BIOL (Biological study)
(hydroxytryptamine uptake inhibition by, paroxetine binding inhibition in relation to, in brain frontal cortex)

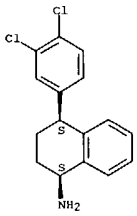
RN 122873-19-2 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 87857-41-8
CMF C16 H15 Cl2 N

Absolute stereochemistry.

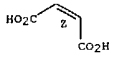
L4 ANSWER 64 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



CM 2

CRN 110-16-7
CMF C4 H4 O4

Double bond geometry as shown.



L4 ANSWER 65 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB Based on mol. cloning studies, five different muscarinic receptor subtypes exist: m1, m2, m3, m4, and m5. The authors determined the affinity and selectivity of binding for sixteen antidepressants, two of their metabolites, and three antihistaminics (H1) at these subtypes. Using Chinese hamster ovary cells (CHO-K1) transfected with genes for the human muscarinic receptor subtypes, the authors obtained equilibrium dissociation consts. (Kds) from competitive radioligand binding studies with [3H]-quinuclidinyl benzilate ([3H]QNB) and membrane prepns. of these cells. QNB was the most potent compound studied (Kd 30-80 pM). Mequitazine (Kd 6-14 nM) and amitriptyline (Kd 7-16 nM) exhibited the highest affinity among the antihistaminics and antidepressants, resp. Among the antidepressants examined were the serotonin-selective drugs sertaline and fluoxetine, both of which displayed Kd values >1 μM. The remaining antidepressants were moderate to weak antagonists with some eliciting no radioligand competition at high concns. The compds. studied showed no significant selectivity among the five cloned subtypes.

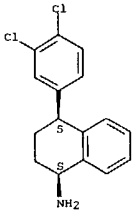
ACCESSION NUMBER: 1993:531407 CAPLUS
DOCUMENT NUMBER: 119:131407
TITLE: Antagonism of the five cloned human muscarinic cholinergic receptors expressed in CHO-K1 cells by antidepressants and antihistaminics
AUTHOR(S): Stanton, Tiffany; Bolden-Watson, Carolyn; Cusack, Bernadette; Richelson, Elliott
CORPORATE SOURCE: Dep. Psychiatry, Mayo Found. and Mayo Clin., Jacksonville, FL, 32224, USA
SOURCE: Biochemical Pharmacology (1993), 45(11), 2352-4
CODEN: BCPCA6; ISSN: 0006-2952
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, Desmethylsertraline
RL: PROC (Process)
(binding of, to human muscarinic receptor subtypes, expressed in Chinese hamster ovary cells)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 65 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

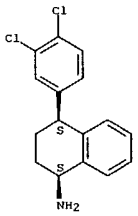


L4 ANSWER 66 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB We determined the uptake blockade produced by eight new antidepressant drugs (etoperidone, femoxetine, lofepramine, nefazodone, paroxetine, sertraline, tomoxetine, and venlafaxine), two metabolites of newer antidepressants, and carbamazepine. Inhibitor consts. (Kis) for uptake blockade were obtained from competitive uptake studies with [3H]norepinephrine, [3H]5-hydroxytryptamine, and [3H]dopamine in rat brain synaptosomes prepared from hippocampus, frontal cortex, and striatum, resp. Among the newer compds., tomoxetine (Ki = 0.7 nM) and lofepramine (Ki = 1.9 nM) were potent and selective]3H]norepinephrine uptake blockers; paroxetine (Ki = 0.73 nM), sertraline (Ki = 3.4 nM), and femoxetine (Ki = 22 nM) potently and selectively inhibited [3H]5-hydroxytryptamine uptake. Although none of the drugs was potent for [3H]dopamine uptake blockade, sertraline was the most potent (Ki = 260 nM). These data are useful in predicting adverse effects and drug-drug interactions of antidepressants.

ACCESSION NUMBER: 1993:183305 CAPLUS
DOCUMENT NUMBER: 118:183305
TITLE: Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes
AUTHOR(S): Bolden-Watson, C.; Richelson, E.
CORPORATE SOURCE: Mayo Clin., Jacksonville, FL, 32224, USA
SOURCE: Life Sciences (1993), 52(12), 1023-9
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: BIOL (Biological study)
(biogenic amine uptake inhibition by, in brain synaptosomes, antidepressant activity in relation to)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

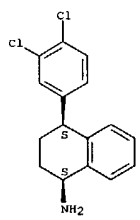


L4 ANSWER 67 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB Some agents that increase serotoninergic transmission in the brain show anorectic activity in doses that do not interfere with the behavior of rats and other animal species. These agents reduce food intake by a mechanism that clearly differs from that involved in the anorectic activity of d-amphetamine. d-Fenfluramine, fluoxetine, and sertraline are three drugs that have already been tested and are used in man. These compds. accumulate in the brain and are metabolized through N-dealkylation. They affect the uptake and release of serotonin at different concns., with mechanisms that do not completely overlap. There is pharmacol. evidence that d-fenfluramine and sertraline exert their anorectic activity by enhancing the stimulation of 5-HT1nonA receptors whereas fluoxetine seems to affect at anorectic doses both serotoninergic and dopaminergic systems. The role of serotonin in controlling food intake will be discussed, and the effects of agents that reduce serotoninergic transmission will also be considered.

ACCESSION NUMBER: 1992:228034 CAPLUS
DOCUMENT NUMBER: 116:228034
TITLE: Progress report on the anorexia induced by drugs believed to mimic some of the effects of serotonin on the central nervous system
AUTHOR(S): Garattini, Silvio; Bizzi, Adalgisa; Codegoni, Anna Maria; Caccia, Silvio; Mennini, Tiziana
CORPORATE SOURCE: Ist. Ric. Farmacol. "Mario Negri", Milan, 20157, Italy
SOURCE: American Journal of Clinical Nutrition (1992), 55(1, Suppl.), 160S-166S
CODEN: AJCNAC; ISSN: 0002-9165
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(sertraline metabolite, anorectic activity of, brain serotoninergic neurotransmission modulation in)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 67 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

L4 ANSWER 68 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

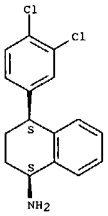
AB A quant. structure-activity relationship (QSAR) was analyzed for monoamine uptake inhibition of cis- and trans-1-alkylamino-4-aryltetralins using the Free-Wilson method. The calculated individual substituent contributions were strongly correlated with the uptake inhibition activity of dopamine, 5-hydroxytryptamine and norepinephrine in the corpus striatum and hypothalamus of rats, resp. The effect of the substituents and stereochem. factors on the monoamine uptake inhibition of the analyzed series of tetralins was discussed.

ACCESSION NUMBER: 1991:526385 CAPLUS
DOCUMENT NUMBER: 115:126385
TITLE: Structure-activity relationship studies of CNS agents. Part II. De novo analysis of the monoamine uptake inhibition data of 1-alkylamino-4-aryltetralins
AUTHOR(S): Mokrosz, Jerzy L.
CORPORATE SOURCE: Inst. Pharmacol., Pol. Acad. Sci., Krakow, 31-343, Pol.
SOURCE: Polish Journal of Pharmacology and Pharmacy (1990), 42(5), 501-7
CODEN: PJPPAA; ISSN: 0301-0244
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **91797-58-9**
RL: BIOL (Biological study)
(monoamines uptake by brain inhibition by, structure in relation to)

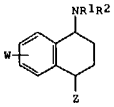
RN 91797-58-9 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L4 ANSWER 69 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

GI



I

AB The title compds. I [R1,R2 = H, C1-3 alkyl; Z = (un)substituted Ph; W = H, F, Br, Cl, CF3, alkoxy] are drugs for treatment of schizophrenia, psychosis, mania, etc., and are also useful as immunosuppressants and inflammation inhibitors. (±)-trans-I (R1 = W = H; R2 = Me; Z = 4-FC6H4) inhibited the in vitro binding of (+)-3-(3-hydroxyphenyl)-N-(1-propyl)piperidine-3H to the σ receptors of the rat brain.

ACCESSION NUMBER: 1991:221410 CAPLUS
DOCUMENT NUMBER: 114:221410
TITLE: 4-Phenyl-1,2,3,4-tetrahydro-1-naphthalenamine derivatives in the treatment of psychosis, inflammation, stroke and as immunosuppressants
INVENTOR(S): Koe, Kenneth B.
PATENT ASSIGNEE(S): Pfizer Inc., USA
SOURCE: Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
EP 386997	A2	19900912	EP 1990-302365		19900306
EP 386997	A3	19920429			
EP 386997	B1	19970319			
R: AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE					
US 4981870	A	19910101	US 1989-320014		19890307
IL 93576	A1	19951208	IL 1990-93576		19900228
CA 2011428	AA	19900907	CA 1990-2011428		19900305
CA 2011428	C	19941108			
AU 9050796	A1	19900920	AU 1990-50796		19900306
AU 610036	B2	19910509			
JP 02300121	A2	19901212	JP 1990-54802		19900306
JP 07014870	B4	19950222			
HU 59000	A2	19920428	HU 1990-1325		19900306
AT 150299	E	19970415	AT 1990-302365		19900306
ZA 9001743	A	19911030	ZA 1990-1743		19900307
US 5061728	A	19911029	US 1990-622308		19901205
JP 07173056	A2	19950711	JP 1994-172929		19940725
PRIORITY APPLN. INFO.:			US 1989-320014	A	19890307

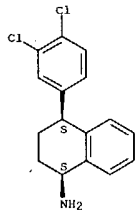
OTHER SOURCE(S): MARPAT 114:221410

L4 ANSWER 69 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

IT **87857-41-8**
RL: BIOL (Biological study)
(pharmaceutical containing, as inflammation and psychosis inhibitor and immunosuppressant)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 70 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB The effects of repeated treatment with the serotonin uptake blocker sertraline on cocaine-induced locomotion in female C57Bl/6ByJ mice were examined in three paradigms. First, when animals were treated for 2 wk with a daily injection of 8 mg/kg i.p. of sertraline (or placebo) and challenged with cocaine (25 mg/kg i.p.) 1 h after the final sertraline injection, their cocaine-induced locomotion was the same as that of placebo-pretreated controls. Second, animals were treated for 2 wk with cocaine (25 mg/kg i.p. once a day) (or saline) and then for 2 wk with sertraline (8 mg/kg i.p. once a day) (or placebo). Locomotion induced by cocaine (25 mg/kg i.p.) administered 1 h after the final sertraline (placebo) injection was higher in cocaine- than saline-pretreated mice (sensitization), but there was no difference between sertraline- and placebo-pretreated animals. Third, daily treatment with sertraline (8 mg/kg i.p.) did not change the locomotor stimulatory effect of cocaine (25 mg/kg i.p.) administered after a 3-wk continuous infusion of cocaine (22 mg/kg/day s.c.) by osmotic minipumps or after three, four, or seven injections of cocaine (15 or 25 mg/kg i.p.). After cocaine administration (25 mg/kg i.p.), animals pretreated repeatly with sertraline (8 mg/kg i.p. once a day for 2 wk) had the same plasma or brain levels of cocaine as those pretreated with placebo; there was no difference between cocaine- and saline-treated mice in brain levels of sertraline or desmethylsertraline.

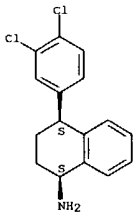
ACCESSION NUMBER: 1991:157119 CAPLUS
DOCUMENT NUMBER: 114:157119
TITLE: Sertraline and cocaine-induced locomotion in mice. II. Chronic studies
AUTHOR(S): Reith, Maarten E. A.; Fischette, Christine T.
CORPORATE SOURCE: Cent. Neurochem., N.S. Kline Inst. Psychiatr. Res., New York, NY, 10035, USA
SOURCE: Psychopharmacology (Berlin, Germany) (1991), 103(3), 306-13
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**, Desmethylsertraline
RL: BIOL (Biological study)
(as sertraline metabolite, cocaine effect on)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 70 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

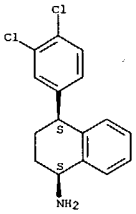


L4 ANSWER 71 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

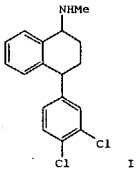
AB The present study assessed the behavioral and pharmacokinetic interaction between the serotonin uptake blocker sertraline and cocaine in C57BL/6ByJ mice. Pretreatment with sertraline (1-32 mg/kg i.p.) did not affect the total amount of spontaneous locomotor activity during 50 min following administration of cocaine (15-40 mg/kg i.p.). At doses of sertraline (16 and 32 mg/kg) much high than those found to inhibit ex vivo neuronal uptake of serotonin by 50% (1-2 mg/kg), the peak of cocaine-induced locomotor activity was shifted towards a later time. A similar effect was seen after pretreatment with serotonin uptake blockers other than sertraline, and also after desipramine. Sertraline (16 and 32 mg/kg), given 60 min prior to cocaine, did not affect levels of cocaine in brain and plasma, and cocaine administration did not alter the brain level of sertraline. Although female mice were more responsive to cocaine than male mice, they were not different in their response to sertraline.

ACCESSION NUMBER: 1991:157118 CAPLUS
DOCUMENT NUMBER: 114:157118
TITLE: Sertraline and cocaine-induced locomotion in mice. I. Acute studies
AUTHOR(S): Reith, Maarten E. A.; Wiener, Harvey L.; Fischette, Christine T.
CORPORATE SOURCE: Cent. Neurochem., N.S. Kline Inst. Psychiatr. Res., New York, NY, 10035, USA
SOURCE: Psychopharmacology (Berlin, Germany) (1991), 103(3), 297-305
CODEN: PSCHDL; ISSN: 0033-3158
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: BIOL (Biological study)
(as sertraline metabolite, cocaine effect on)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 72 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
GI



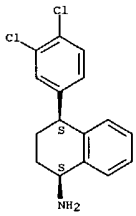
I

AB A rapid isocratic reversed-phase HPLC method for simultaneous determination of sertraline (I) and its metabolite desmethylsertraline (II) in mouse cerebral cortex is described. The method is based on a Versapack C18 10-μm-column, MeCN-0.25M KH2PO4 (pH 2.7) buffer (30:70), the flow rate of 2 mL/min, and tetracaine as an internal standard The retention time was 9.5 and 12 min for II and I, resp. Standard curves for I and II were linear and had the following regression coeffs.: for I: slope = 0.105, y-axiss intercept = -0.8, r2 = 0.998; for II; slope = 0.11, y-axis intercept = 1.37, r2 = 0.989. After one extraction with EtOH, 89% of the I and 87% of the II was recovered. The coefficient of variations for I and II was 4.8 and 4.9%, resp. After i.p. administration of 32 mg/kg I, the drug was detectable as early as 5 min after injection. The metabolite was first observed 15 min after administration of I. The detection limit was .apprx.20 and 10 pmol/mg wet weight for I and II, resp.

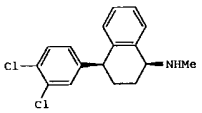
ACCESSION NUMBER: 1990:508607 CAPLUS
DOCUMENT NUMBER: 113:108607
TITLE: Separation and determination of sertraline and its metabolite, desmethylsertraline, in mouse cerebral cortex by reversed-phase high-performance liquid chromatography
AUTHOR(S): Wiener, Harvey L.; Kramer, H. Kenneth; Reith, Maarten E. A.
CORPORATE SOURCE: Coll. Pharm. Allied Health Prof., St. John's Univ., Jamaica, NY, 11439, USA
SOURCE: Journal of Chromatography (1990), 527(2), 467-72
CODEN: JOCRAM; ISSN: 0021-9673
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**, Desmethylsertraline
RL: ANT (Analyte); ANST (Analytical study)
(determination of, as sertraline metabolite, in cerebral cortex, by reversed-phase HPLC)
RN 87857-41-8 CAPLUS

L4 ANSWER 72 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 73 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
GI



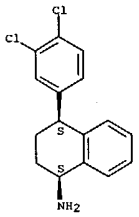
I

AB Sertraline (I) is a potent and selective inhibitor of neuronal serotonin uptake and is currently under development for the treatment of depression and of obesity. The drug was >97% bound to plasma proteins, yet extensively distributed into tissues. The whole brain concentration of sertraline in the rat was >40-fold higher than that in plasma, and the volume of distribution was about 25 L/kg in the rat and dog. Sertraline was extensively metabolized by the rat and dog prior to excretion. The metabolic clearance of sertraline was >35 mL of blood/min/kg in each species, and 1st-pass metabolism occurred with oral administration. Initial metabolic steps included N-demethylation, N-hydroxylation, oxidative deamination, and glucuronidation of sertraline carbamic acid, which in solution was in equilibrium with sertraline and CO2. The N-demethyl metabolite, which was 10-fold less potent as an inhibitor of serotonin uptake, was formed in both species. Plasma area under the concentration-time curve for demethylsertraline was 66-270% of that for sertraline, and was dependent on the species examined and route of drug administration. Sertraline and demethylsertraline underwent oxidative deamination to the corresponding ketone, which was subsequently hydroxylated at the α-carbon, forming a diastereomeric metabolite pair. The glucuronides of sertraline carbamic acid, N-hydroxysertraline, and the α-hydroxy ketone diastereomers comprised 45% and 82% of the total radiolabel excreted in urine plus bile of duct-cannulated rats and dogs, resp. Bile was the major route of elimination in both species.

ACCESSION NUMBER: 1990:15883 CAPLUS
DOCUMENT NUMBER: 112:15883
TITLE: Metabolism and disposition of the 5-hydroxytryptamine uptake blocker sertraline in the rat and dog
AUTHOR(S): Tremaine, Larry M.; Welch, Willard M.; Ronfeld, Robert A.
CORPORATE SOURCE: Drug Metab. Dep., Pfizer, Inc., Groton, CT, USA
SOURCE: Drug Metabolism and Disposition (1989), 17(5), 542-50
CODEN: DMDSAI; ISSN: 0090-9556
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8P**, Demethylsertraline
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and formation of, as sertraline metabolite)

L4 ANSWER 73 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



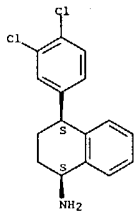
L4 ANSWER 74 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
AB [N-methyl-11C]Sertraline, a potential agent for the study of the serotonergic system in vivo with positron emission tomog., was prepared by N-methylation of the corresponding norcompound with [11C]iodomethane, which was itself prepared form cyclotron-produced [11C]carbon dioxide. Under the best conditions found [norsertraline free base (20 mM) in DMF (0.70 mL), 120° for 8 min] [N-methyl-11C]sertraline can be prepared in 43% radiochem. yield from [11C]iodomethane (decay-corrected), corresponding to 20% overall radiochem. yield from [11C]carbon dioxide (decay-corrected), with high specific radioactivity. Prepns. can be ready for i.v. injection 50 min from the end of radionuclide production

ACCESSION NUMBER: 1989:553324 CAPLUS
DOCUMENT NUMBER: 111:153324
TITLE: The radiosynthesis of [N-methyl-11C]-sertraline
AUTHOR(S): Lasne, M. C.; Pike, V. W.; Turton, D. R.
CORPORATE SOURCE: MRC Cyclotron Unit, Hammersmith Hosp., London, W12 0HS, UK
SOURCE: Applied Radiation and Isotopes (1989), 40(2), 147-51
CODEN: ARISEF; ISSN: 0883-2889
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **122873-19-2**, Norsertraline maleate
RL: PROC (Process)
(conversion of, to norsertraline free base)
RN 122873-19-2 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-, (2Z)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

CRN 87857-41-8
CMF C16 H15 Cl2 N

Absolute stereochemistry.

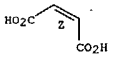


CM 2

CRN 110-16-7

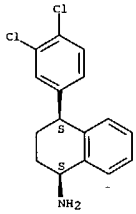
L4 ANSWER 74 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
CMF C4 H4 O4

Double bond geometry as shown.



IT **87857-41-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 75 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

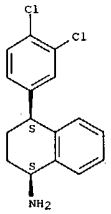
AB QSAR of monoamine uptake inhibition by cis- and trans-1-amino-4-aryltetralins was examined Physicochem. parameters such as electronic (σ), hydrophobic (π), and molar refraction (MR) were significantly correlated with 5-HT [50-67-9] uptake inhibition in corpus striatum of rat brain for both series of compds. The norepinephrine (NE) [51-41-2] uptake inhibition in hypothalamus and dopamine (DA) [51-61-6] uptake inhibition in corpus striatum, however, yielded poor correlations with either set of compds. However, the selectivity ratios, -log [IC50 (DA)/IC50 (5-HT)] and -log [IC50 (NE)/IC50 (5-HT)] described statistically sound correlations with properly chosen physicochem. parameters for cis- and trans-1-amino-4-aryltetralins.

ACCESSION NUMBER: 1987:148963 CAPLUS
DOCUMENT NUMBER: 106:148963
TITLE: Quantitative structure-activity relationship of antidepressant agents. Derivatives of cis- and trans-1-amino-4-aryltetralin
AUTHOR(S): Singh, P.; Goyal, A.
CORPORATE SOURCE: Dep. Chem., Birla Inst. Technol. Sci., Pilani, India
SOURCE: Arzneimittel-Forschung (1987), 37(1), 51-4
CODEN: ARZNAD; ISSN: 0004-4172
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **91797-58-9**
RL: BIOL (Biological study)
(brain monoamine uptake inhibition by, QSAR of)

RN 91797-58-9 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L4 ANSWER 76 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

AB The effects of 2 specific serotonin re-uptake inhibitors, sertraline [79617-96-2] and Organic 6582 [59905-71-4], on the behavior of the bilaterally olfactory bulbectomized rat in the open field apparatus were compared following their acute and chronic administration. Neither drug affected the increased ambulation scores of the bulbectomized rats following their acute administration, but both drugs significantly attenuated the hypermotility of the bulbectomized rats after chronic (12 d) administration. Only Organic 6582 reduced the increased rearing score in the open field are qual. similar to that found in other studies for both typical (e.g., amitriptyline) and atypical (e.g., mianserin) antidepressants. The major metabolite of sertraline, CP-53261 (desmethylsertraline) **[87857-41-8]** was inactive in this behavioral test. The effects of sertraline on the behavior of rats in the hole board apparatus was also assessed. Sertraline, after both its acute and chronic administration, increased the number of crossings of the bulbectomized rats, without affecting the sham-operated controls. Unlike the stressful open field apparatus, the less stressful hole board apparatus cannot be used to differentiate between the bulbectomized rats, their sham-operated controls and the chronic effect of antidepressants. Organic 6582 increased the serotonin [50-67-9] content of the mid-brain of the bulbectomized rats and reduced that of 5-HIAA, without appreciably affecting the concns. of GABA [56-12-2], noradrenaline [51-41-2] and sertonin in the amygdaloid cortex or mid-brain. By contrast, sertraline increased the dopamine [51-61-6] concentration in the amygdaloid cortex of the sham-operated and bulbectomized rats and raised the serotonin content of the mid-brain without affecting that of 5-HIAA. Apparently the attenuation of the hypermotility in the open filed apparatus might be correlated with a rise in the serotonin content in this region. The relation of these results to the antidepressant activity of sertraline and Organic 6582 and the use of olfactory bulbectomized rats as an animal model of depression are discussed.

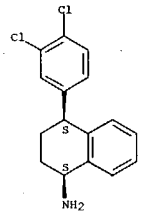
ACCESSION NUMBER: 1986:199968 CAPLUS
DOCUMENT NUMBER: 104:199968
TITLE: Effect of two specific serotonin re-uptake inhibitors on the behavior of the olfactory bulbectomized rat in the 'open field' apparatus
AUTHOR(S): Earley, Bernadette; Leonard, B. E.
CORPORATE SOURCE: Pharmacol. Dep., Univ. Coll. Galway, Galway, Ire.
SOURCE: Biological Psychiatry--New Prospects (1985), 5(Clin. Pharmacol. Stud. Psychiatr. Disord.), 234-40
CODEN: BPNPES; ISSN: 0266-2124
DOCUMENT TYPE: Journal
LANGUAGE: English

IT **87857-41-8**
RL: BIOL (Biological study)
(hyperkinesis in olfactory bulbectomized rat response to, antidepressant activity in relation to, as sertraline metabolite)

RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)- (9CI) (CA INDEX NAME)

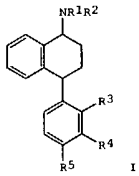
L4 ANSWER 76 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

Absolute stereochemistry.



L4 ANSWER 77 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN

GI



I

AB The title compound enantiomers I (R1 and R2 = H or Me; R3 = H, Cl, or MeO; R4 = H, Cl, CF3, or MeO; R5 = H, Br, Cl, F, CF3, MeO, BuO, or PhO) mostly as the HCl salts were prepared from the appropriate benzophenone and 136 1-tetralone [52758-06-2] and evaluated in vitro for their ability to inhibit the uptake of dopamine and serotonin in corpus striatum and of epinephrine in hypothalamus of rats. The cis compds. are potent and selective inhibitors of serotonin uptake, whereas the trans compds. block uptake of dopamine and norepinephrine. Structure-activity relations are discussed.

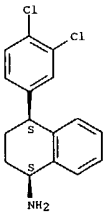
ACCESSION NUMBER: 1984:622093 CAPLUS
DOCUMENT NUMBER: 101:222093
TITLE: Nontricyclic antidepressant agents derived from cis- and trans-1-amino-4-aryltetralins
AUTHOR(S): Welch, Willard M.; Kraska, Allen R.; Sarges, Reinhard; Koe, B. Kenneth
CORPORATE SOURCE: Cent. Res. Div., Pfizer Inc., Groton, CT, 06340, USA
SOURCE: Journal of Medicinal Chemistry (1984), 27(11), 1508-15
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 101:222093

IT **91797-58-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(monoamine uptake by brain response to)

RN 91797-58-9 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, cis- (9CI) (CA INDEX NAME)

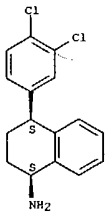
Relative stereochemistry.

L4 ANSWER 77 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



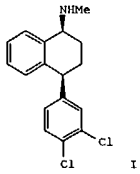
IT **91797-57-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and monoamine uptake by brain response to)
RN 91797-57-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, hydrochloride, cis- (9CI) (CA INDEX NAME)

Relative stereochemistry.



● HCl

L4 ANSWER 78 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
GI



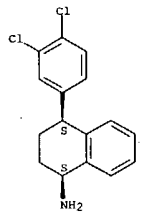
I

AB The pharmacol. activity of sertraline (I) [79617-96-2] was evaluated in tests predictive of 5-HT [50-67-9] uptake inhibiting and antidepressant activity. I is a highly selective and potent inhibitor of synaptosomal 5-HT uptake in rat brain. N-Demethylsertraline **[87857-41-8]**, the major metabolite of I, is also a selective 5-HT uptake blocker, indicating that this selective inhibition is probably maintained in vivo. I markedly reduced the immobility of mice in the Porsolt forced swimming test; in addition repeated dosing of I induced down regulation of norepinephrine coupled adenylate cyclase in rat limbic forebrain. Thus, I should be clin. effective as an antideppressant.

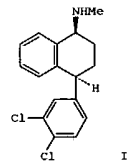
ACCESSION NUMBER: 1984:45134 CAPLUS
DOCUMENT NUMBER: 100:45134
TITLE: Sertraline: a new selective inhibitor of serotonin uptake
AUTHOR(S): Koe, B. Kenneth; Weissman, Albert; Welch, Willard M.; Browne, Ronald G.
CORPORATE SOURCE: Cent. Res. Div., Pfizer Inc., Groton, CT, 06340, USA
SOURCE: Psychopharmacology Bulletin (1983), 19(4), 687-91
CODEN: PSYBB9; ISSN: 0048-5764
DOCUMENT TYPE: Journal
LANGUAGE: English
IT **87857-41-8**
RL: BIOL (Biological study)
(sertraline metabolite, serotonin uptake by brain inhibition by)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 78 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



L4 ANSWER 79 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN
GI



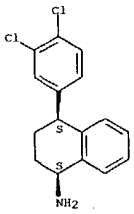
I

AB Sertraline (I) [79617-96-2] was highly selective and potent competitive inhibitor of synaptosomal serotonin [50-67-9] uptake. I also selectively reduced ex vivo uptake of I and strongly antagonized the serotonin-depleting action of p-chloroamphetamine, indicating potent blockade of serotonin uptake in vivo. Acute and repeated dosing of I decreased serotonin content of whole blood. I only weakly inhibited rat heart uptake of i.v. 3H-labeled norepinephrine [51-41-2]. In substantiation of selective blockade of serotonin uptake, I potentiated various symptoms of 5-hydroxytryptophan but did not reverse reserpine-induced hypothermia. I was a very weak inhibitor of [3H]quinuclidinyl benzilate binding to rat brain membranes in vitro and did not produce anticholinergic effects in mice in vivo. I was well tolerated in mice, rats and dogs, with no locomotor stimulant effects in rats or untoward cardiovascular effects in dogs. The major metabolite, N-desmethylsertraline **[87857-41-8]** was also a selective serotonin uptake blocker. I strongly reduced immobility of mice in the Porsolt swim test for antidepressants. After repeated dosing in rats, I diminished the cyclic AMP [60-92-4] response of limbic forebrain adenylate cyclase [9012-42-4] to norepinephrine, as well as the binding of [3H]dihydroalprenolol to cortical membranes. It is proposed that selective blockade of serotonin reuptake can induce activation of norepinephrine neurons and subsequent down-regulation of norepinephrine receptors and that I, a highly selective inhibitor of serotonin uptake, may be an efficacious antidepressant without anticholinergic or cardiovascular side-effects.

ACCESSION NUMBER: 1984:17488 CAPLUS
DOCUMENT NUMBER: 100:17488
TITLE: Sertraline, 1S,4S-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthylamine, a new uptake inhibitor with selectivity for serotonin
AUTHOR(S): Koe, B. Kenneth; Weissman, Albert; Welch, Willard M.; Browne, Ronald G.
CORPORATE SOURCE: Cent. Res. Div., Pfizer Inc., Groton, CT, 06340, USA
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1983), 226(3), 686-700
CODEN: JPETAB; ISSN: 0022-3565
DOCUMENT TYPE: Journal
LANGUAGE: English

L4 ANSWER 79 OF 79 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
IT **87857-41-8**
RL: BIOL (Biological study)
(as sertraline metabolite, serotonin uptake inhibition by, antidepressant activity in relation to)
RN 87857-41-8 CAPLUS
CN 1-Naphthalenamine, 4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-, (1S,4S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> fil reg
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	380.88	536.51

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-55.30	-55.30

FILE 'REGISTRY' ENTERED AT 21:51:39 ON 14 NOV 2004
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 12 NOV 2004 HIGHEST RN 780001-49-2
DICTIONARY FILE UPDATES: 12 NOV 2004 HIGHEST RN 780001-49-2

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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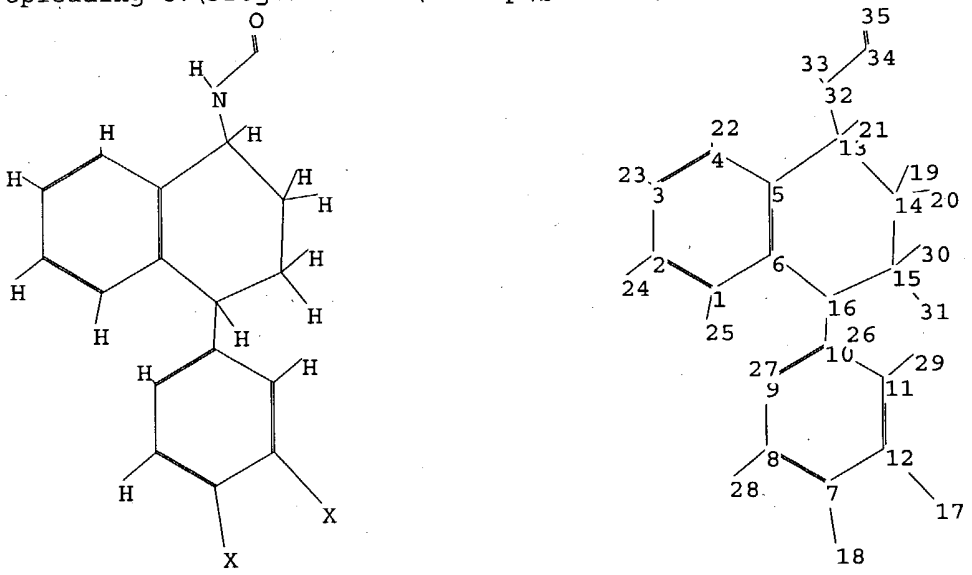
Uploading C:\Program Files\Stnexp\Queries\10663173.str



chain nodes :
17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35
ring nodes :

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1  2  3  4  5  6  7  8  9  10  11  12  13  14  15  16
chain bonds :
1-25  2-24  3-23  4-22  7-18  8-28  9-27  10-16  11-29  12-17  13-21  13-32  14-19
14-20  15-30  15-31  16-26  32-33  32-34  34-35
ring bonds :
1-2  1-6  2-3  3-4  4-5  5-6  5-13  6-16  7-8  7-12  8-9  9-10  10-11  11-12  13-14
 14-15  15-16
exact/norm bonds :
5-13  6-16  13-14  13-32  14-15  15-16  32-34  34-35
exact bonds :
1-25  2-24  3-23  4-22  7-18  8-28  9-27  10-16  11-29  12-17  13-21  14-19  14-20
15-30  15-31  16-26  32-33
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6  7-8  7-12  8-9  9-10  10-11  11-12


Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom
11:Atom  12:Atom  13:Atom  14:Atom  15:Atom  16:Atom  17:CLASS  18:CLASS  19:CLASS
20:CLASS  21:CLASS  22:CLASS  23:CLASS  24:CLASS  25:CLASS  26:CLASS  27:CLASS
28:CLASS  29:CLASS  30:CLASS  31:CLASS  32:CLASS  33:CLASS  34:CLASS  35:CLASS



L5      STRUCTURE UPLOADED

=> d query
L5              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.


=> s l5
SAMPLE SEARCH INITIATED 21:53:00 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -     677 TO ITERATE

100.0% PROCESSED     677 ITERATIONS                                    0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:        11979 TO    15101
PROJECTED ANSWERS:               0 TO        0

L6            0 SEA SSS SAM L5

=> s l5 full
FULL SEARCH INITIATED 21:53:04 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -  13751 TO ITERATE

100.0% PROCESSED   13751 ITERATIONS                                    5 ANSWERS
SEARCH TIME: 00.00.01

L7            5 SEA SSS FUL L5

=> fil caplus
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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	155.84	692.35

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-55.30

FILE 'CAPLUS' ENTERED AT 21:53:07 ON 14 NOV 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 14 Nov 2004 VOL 141 ISS 21
FILE LAST UPDATED: 12 Nov 2004 (20041112/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l7
L8 2 L7

=> d l8 1-2 abs ibib hitstr

L8 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN

AB Trans-, (1R,4S)-, and (1S,4R)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamines are claimed. In functional monoamine uptake inhibition assays for serotonin, norepinephrine, and dopamine, the (1R,4S)- isomer showed IC50 = 0.0077, 0.0096, and 0.0064 μM, resp.

ACCESSION NUMBER: 2004:252469 CAPLUS
DOCUMENT NUMBER: 140:287185
TITLE: Preparation of trans-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenamine for treatment of CNS disorders.
INVENTOR(S): Jerussi, Thomas P.; Fang, Qun Kevin; Currie, Mark
PATENT ASSIGNEE(S): Sepracor, Inc., USA
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004024669	A1	20040325	WO 2003-US29110	20030916
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004092605	A1	20040513	US 2003-663173	20030916
PRIORITY APPLN. INFO.:			US 2002-411304P P	20020916
			US 2002-411305P P	20020916

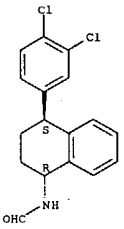
OTHER SOURCE(S): CASREACT 140:287185

IT **675126-11-1 675126-12-2**
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of dichlorophenyltetrahydronaphthalenamines for treatment of CNS disorders)

RN 675126-11-1 CAPLUS
CN Formamide, N-[(1R,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]- (9CI) (CA INDEX NAME)

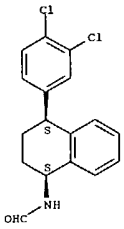
Absolute stereochemistry.

L8 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RN 675126-12-2 CAPLUS
CN Formamide, N-[(1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

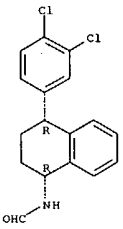


IT **674768-11-7P 674768-15-1P 674768-49-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of dichlorophenyltetrahydronaphthalenamines for treatment of CNS disorders)

RN 674768-11-7 CAPLUS
CN Formamide, N-[(1R,4R)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]- (9CI) (CA INDEX NAME)

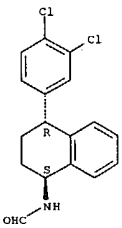
Absolute stereochemistry.

L8 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



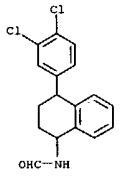
RN 674768-15-1 CAPLUS
CN Formamide, N-[(1S,4R)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 674768-49-1 CAPLUS
CN Formamide, N-[4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]- (9CI) (CA INDEX NAME)

L8 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN

AB Treatment of central nervous system disorders with (1R,4S)-trans- (I) and (1S,4R)-trans-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine (II) is disclosed. I and II were prepared by treating 4-(3,4-dichlorophenyl)tetralinone (III) with (R)-Me3CS(O)NH2 to give the imines which were separated, hydrolyzed to (R)-III and (S)-III, treated with HCONH2 to give the formamides, which were separated by flash chromatog. and reduced with BH3 to give I and II. I and II had IC50 for 5-HT uptake of 0.0075 and 0.012 μM, resp.

ACCESSION NUMBER: 2004:252329 CAPLUS
DOCUMENT NUMBER: 140:270634
TITLE: Treatment of CNS disorders with trans-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine
INVENTOR(S): Jerussi, Thomas P.; Fang, Qun Kevin; Currie, Mark
PATENT ASSIGNEE(S): Sepracor, Inc., USA
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004024130	A2	20040325	WO 2003-US29112	20030916
WO 2004024130	A3	20040715		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004087661	A1	20040506	US 2003-662997	20030916
PRIORITY APPLN. INFO.:			US 2002-411303P P	20020916

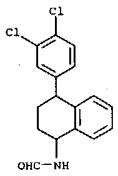
OTHER SOURCE(S): CASREACT 140:270634; MARPAT 140:270634

IT **674768-11-7P 674768-15-1P 674768-49-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of (1R,4S)-trans- and (1S,4R)trans-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthalenamine for treatment of CNS disorders)

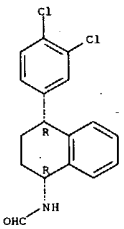
RN 674768-11-7 CAPLUS
CN Formamide, N-[(1R,4R)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L8 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

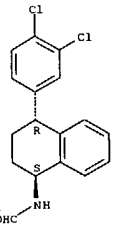


L8 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RN 674768-15-1 CAPLUS
CN Formamide, N-[(1S,4R)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 674768-49-1 CAPLUS
CN Formamide, N-[4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]- (9CI) (CA INDEX NAME)

=> fil reg
COST IN U.S. DOLLARS

	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	10.84	703.19

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-1.40	-56.70

FILE 'REGISTRY' ENTERED AT 21:55:02 ON 14 NOV 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 12 NOV 2004 HIGHEST RN 780001-49-2
DICTIONARY FILE UPDATES: 12 NOV 2004 HIGHEST RN 780001-49-2

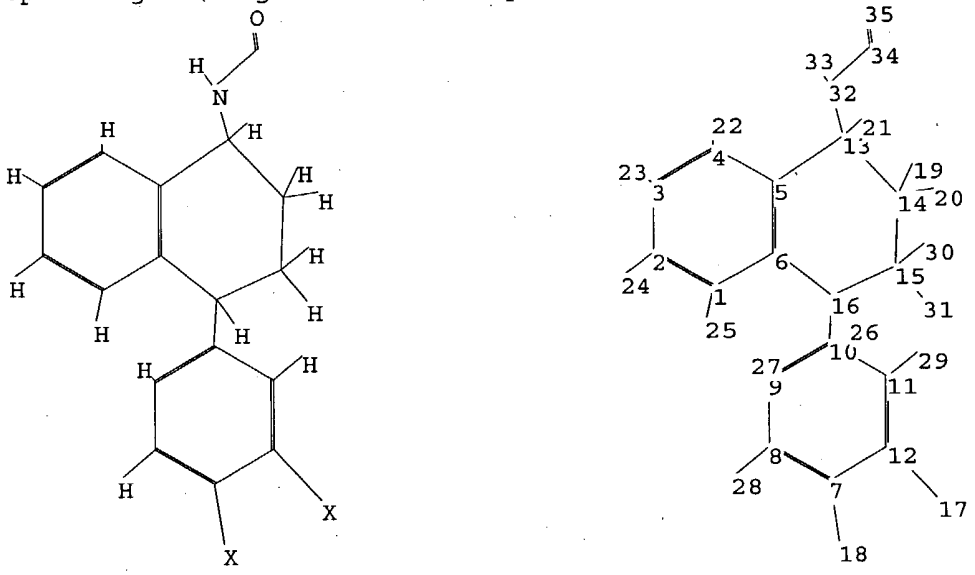
TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=>
Uploading C:\Program Files\Stnexp\Queries\10663173.str



chain nodes :
17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35
ring nodes :

```
1  2  3  4  5  6  7  8  9  10  11  12  13  14  15  16
chain bonds :
1-25  2-24  3-23  4-22  7-18  8-28  9-27  10-16  11-29  12-17  13-21  13-32  14-19
14-20  15-30  15-31  16-26  32-33  32-34  34-35
ring bonds :
1-2  1-6  2-3  3-4  4-5  5-6  5-13  6-16  7-8  7-12  8-9  9-10  10-11  11-12  13-14
 14-15  15-16
exact/norm bonds :
5-13  6-16  13-14  13-32  14-15  15-16  32-34  34-35
exact bonds :
1-25  2-24  3-23  4-22  7-18  8-28  9-27  10-16  11-29  12-17  13-21  14-19  14-20
15-30  15-31  16-26  32-33
normalized bonds :
1-2  1-6  2-3  3-4  4-5  5-6  7-8  7-12  8-9  9-10  10-11  11-12


Match level :
1:Atom  2:Atom  3:Atom  4:Atom  5:Atom  6:Atom  7:Atom  8:Atom  9:Atom  10:Atom
11:Atom  12:Atom  13:Atom  14:Atom  15:Atom  16:Atom  17:CLASS  18:CLASS  19:CLASS
20:CLASS  21:CLASS  22:CLASS  23:CLASS  24:CLASS  25:CLASS  26:CLASS  27:CLASS
28:CLASS  29:CLASS  30:CLASS  31:CLASS  32:CLASS  33:CLASS  34:CLASS  35:CLASS



L9      STRUCTURE UPLOADED

=> d query
L9              STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -  AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation.


=> s l9
SAMPLE SEARCH INITIATED 21:55:31 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED -    677 TO ITERATE

100.0% PROCESSED     677 ITERATIONS                                  0 ANSWERS
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **COMPLETE**
                        BATCH   **COMPLETE**
PROJECTED ITERATIONS:        11979 TO    15101
PROJECTED ANSWERS:               0 TO        0

L10           0 SEA SSS SAM L9

=> s l9 full
FULL SEARCH INITIATED 21:55:34 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -  13751 TO ITERATE

100.0% PROCESSED   13751 ITERATIONS                                 11 ANSWERS
SEARCH TIME: 00.00.01

L11          11 SEA SSS FUL L9

=> fil caplus
```

```
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                          ENTRY     SESSION
FULL ESTIMATED COST                                      155.42      858.61

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)              SINCE FILE      TOTAL
                                                          ENTRY     SESSION
CA SUBSCRIBER PRICE                                        0.00      -56.70

FILE 'CAPLUS' ENTERED AT 21:55:38 ON 14 NOV 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)
```



```
FILE COVERS 1907 - 14 Nov 2004  VOL 141 ISS 21
FILE LAST UPDATED: 12 Nov 2004  (20041112/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


=> s l11
L12           7 L11

=> d his

     (FILE 'HOME' ENTERED AT 21:44:25 ON 14 NOV 2004)

     FILE 'REGISTRY' ENTERED AT 21:44:32 ON 14 NOV 2004
L1               STRUCTURE UPLOADED
L2             0 S L1
L3            12 S L1 FULL

     FILE 'CAPLUS' ENTERED AT 21:44:55 ON 14 NOV 2004
L4            79 S L3

     FILE 'REGISTRY' ENTERED AT 21:51:39 ON 14 NOV 2004
L5               STRUCTURE UPLOADED
L6             0 S L5
L7             5 S L5 FULL

     FILE 'CAPLUS' ENTERED AT 21:53:07 ON 14 NOV 2004
L8             2 S L7

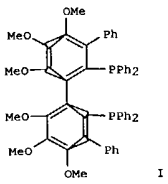
     FILE 'REGISTRY' ENTERED AT 21:55:02 ON 14 NOV 2004
L9               STRUCTURE UPLOADED
L10            0 S L9
L11           11 S L9 FULL
```

```
     FILE 'CAPLUS' ENTERED AT 21:55:38 ON 14 NOV 2004
L12             7 S L11

=> s l12 not l8
L13             5 L12 NOT L8

=> d l13 1-5 abs ibib hitstr
```

L13 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
GI



I

AB An ortho-substituted BIPHEP ligand, o-Ph-hexaMeO-BIPHEP (I), is designed and synthesized. Compared with chiral biarylphosphines without ortho substituents such as BINAP and MeO-BIPHEP, I shows higher enantioselectivities in Rh-catalyzed hydrogenation of cyclic enamides.

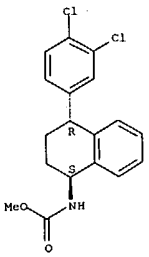
ACCESSION NUMBER: 2002:308267 CAPLUS
DOCUMENT NUMBER: 137:46985
TITLE: An ortho-Substituted BIPHEP Ligand and Its Applications in Rh-Catalyzed Hydrogenation of Cyclic Enamides
AUTHOR(S): Tang, Wenjun; Chi, Yongxiang; Zhang, Xumu
CORPORATE SOURCE: Department of Chemistry, The Pennsylvania State University, University Park, PA, 16802, USA
SOURCE: Organic Letters (2002), 4(10), 1695-1698
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:46985

IT **438456-02-1P 438456-04-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(an ortho-substituted BIPHEP ligand and its applications in Rh-catalyzed hydrogenation of cyclic enamides)

RN 438456-02-1 CAPLUS
CN Carbamic acid, [(1S,4R)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]-, methyl ester (9CI) (CA INDEX NAME)

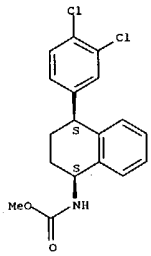
Absolute stereochemistry. Rotation (-).

L13 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RN 438456-04-3 CAPLUS
CN Carbamic acid, [(1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L13 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
AB Intramol. endo-cyclization reactions of N-acyliminium ions have seen wide application for the synthesis of heterocyclic compds. The corresponding exocyclic variant, which would provide 1-aminotetralin derivs., for example, has little precedent. The authors have discovered that acyclic N-acylcarbamates can be readily reduced to the corresponding N-acylhemiaminal derivs. in high yield using DIBAL as the reducing agent. These intermediates are remarkably stable and, if desired, can be purified and stored. The acyclic N-acylhemiaminals undergo both intra- and intermol. nucleophilic addition reactions mediated by strong Lewis acids, such as TiCl4. Diastereoselectivity, induced either by a substituent on the newly formed ring, or by utilizing a chiral ester on the carbamic acid, was disappointingly low. This methodol. was successfully applied to the synthesis of the racemic form of the marketed antidepressant sertraline.

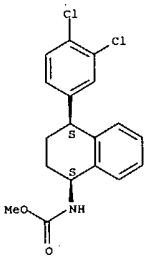
ACCESSION NUMBER: 2001:695659 CAPLUS
DOCUMENT NUMBER: 136:19916
TITLE: The Preparation and Intra- and Intermolecular Addition Reactions of Acyclic N-Acylimines: Application to the Synthesis of (±)-Sertraline
AUTHOR(S): DeNinno, Michael P.; Eller, Cynthia; Etienne, John B.
CORPORATE SOURCE: PGRD Groton Laboratories, Pfizer Inc., Groton, CT, 06340, USA
SOURCE: Journal of Organic Chemistry (2001), 66(21), 6988-6993
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 136:19916

IT **374778-34-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and intra- and intermol. addition reactions of acyclic N-acylimines)

RN 374778-34-4 CAPLUS
CN Carbamic acid, [(1R,4R)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]-, methyl ester, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

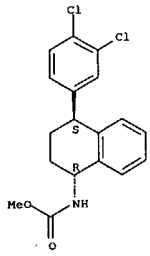
L13 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



IT **374778-36-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and intra- and intermol. addition reactions of acyclic N-acylimines)

RN 374778-36-6 CAPLUS
CN Carbamic acid, [(1R,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]-, methyl ester, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

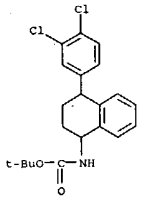
L13 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

AB N-(tert-butoxycarbonyl) amines are directly obtained from oximes of aldehydes and ketones in one-pot when treated with polymethylhydrosiloxane (PMHS) and di-tert-Bu dicarbonate in the presence of catalytic amount of 10% Pd-C for the first time.

ACCESSION NUMBER: 2000:700758 CAPLUS
DOCUMENT NUMBER: 134:4524
TITLE: One-pot conversion of oximes to N-(tert-butoxycarbonyl) amines with polymethylhydrosiloxane, Pd-C and di-tert-butyl dicarbonate
AUTHOR(S): Chandrasekhar, S.; Reddy, M. Venkat; Chandraiah, L.
CORPORATE SOURCE: Indian Institute of Chemical Technology, Hyderabad, 500 007, India
SOURCE: Synlett (2000), (9), 1351-1353
CODEN: SYNLES; ISSN: 0936-5214
PUBLISHER: Georg Thieme Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 134:4524

IT **296778-54-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(one-pot conversion of oximes to N-(tert-butoxycarbonyl) amines with polymethylhydrosiloxane, Pd-C, and di-tert-Bu dicarbonate)

RN 296778-54-6 CAPLUS
CN Carbamic acid, [4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

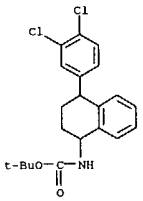
L13 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

AB One step direct conversion of azides and benzyl carbamates to t-Bu carbamates is achieved using inexpensive and safe hydride source polymethylhydrosiloxane (PMHS) under Pd-C catalysis.

ACCESSION NUMBER: 2000:488616 CAPLUS
DOCUMENT NUMBER: 133:266272
TITLE: Direct conversion of azides and benzyl carbamates to t-butyl carbamates using polymethylhydrosiloxane and Pd-C
AUTHOR(S): Chandrasekhar, S.; Chandraiah, L.; Reddy, Ch. Raji; Reddy, M. Venkat
CORPORATE SOURCE: Indian Institute of Chemical Technology, Hyderabad, 500 007, India
SOURCE: Chemistry Letters (2000), (7), 780-781
CODEN: CMLTAG; ISSN: 0366-7022
PUBLISHER: Chemical Society of Japan
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 133:266272

IT **296778-54-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(direct conversion of azides and benzyl carbamates to t-Bu carbamates using polymethylhydrosiloxane and Pd-C)

RN 296778-54-6 CAPLUS
CN Carbamic acid, [4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L13 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

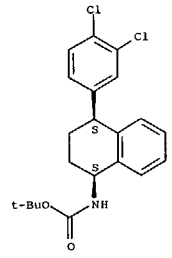
AB An efficient and practical total synthesis of cis-(+)-sertraline is developed involving intramol. Friedel-Crafts cyclization of an appropriately tailored D-phenylglycine.

ACCESSION NUMBER: 2000:147120 CAPLUS
DOCUMENT NUMBER: 132:334264
TITLE: An expedient total synthesis of cis-(+)-sertraline from D-phenylglycine
AUTHOR(S): Chandrasekhar, S.; Reddy, M. Venkat
CORPORATE SOURCE: Indian Institute of Chemical Technology, Hyderabad, 500007, India
SOURCE: Tetrahedron (2000), 56(8), 1111-1114
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 132:334264

IT **267884-84-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(total synthesis of sertraline from phenylglycine)

RN 267884-84-4 CAPLUS
CN Carbamic acid, [(1S,4S)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

```
=> logoff y
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    25.12     883.73

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -3.50     -60.20

STN INTERNATIONAL LOGOFF AT 21:57:41 ON 14 NOV 2004
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